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(54) Title: GENES, COMPOSITIONS, KITS, AND METHOD FOR IDENTIFICATION, ASSESSMENT, PREVENTION AND THERAPY OF OVARIAN CANCER

(57) Abstract: The invention relates to compositions, kits, and methods for detecting, characterizing, preventing, and treating human ovarian cancers. A variety of novel markers are provided, wherein changes in the levels of expression of one or more of the markers is correlated with the presence of ovarian cancer.

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COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF OVARIAN CANCER

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RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/191,031 filed on March 21, 2000, U.S. provisional patent application serial no. 60/207,124, filed on May 25, 2000, U.S. provisional patent application serial no. 60/211,940, filed on June 15, 2000, U.S. provisional patent application serial no. 60/216,820, filed on July 7, 2000, U.S. provisional patent application serial no. 60/220,661, filed on July 25, 2000, and U.S. provisional patent application serial no. 60/257,672, filed on December 21, 2000, all of which are expressly incorporated by reference.

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FIELD OF THE INVENTION

The field of the invention is ovarian cancer, including diagnosis, characterization, management, and therapy of ovarian cancer.

BACKGROUND OF THE INVENTION

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Ovarian cancer is responsible for significant morbidity and mortality in populations around the world. Ovarian cancer is classified, on the basis of clinical and pathological features, in three groups, namely epithelial ovarian cancer (EOC; >90% of ovarian cancer in Western countries), germ cell tumors (circa 2-3% of ovarian cancer), and stromal ovarian cancer (circa 5% of ovarian cancer; Ozols et al., 1997, Cancer Principles and Practice of Oncology, 5th ed., DeVita et al., Eds. pp. 1502). Relative to EOC, germ cell tumors and stromal ovarian cancers are more easily detected and treated at an early stage, translating into higher/better survival rates for patients afflicted with these two types of ovarian cancer.

There are numerous types of ovarian tumors, some of which are benign, and others of which are malignant. Treatment (including non-treatment) options and predictions of patient outcome depend on accurate classification of the ovarian cancer. Ovarian cancers are named according to the type of cells from which the cancer is

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derived and whether the ovarian cancer is benign or malignant. Recognized histological tumor types include, for example, serous, mucinous, endometrioid, and clear cell tumors. In addition, ovarian cancers are classified according to recognized grade and stage scales.

5 In grade I, the tumor tissue is well differentiated from normal ovarian tissue. In grade II, tumor tissue is moderately well differentiated. In grade III, the tumor tissue is poorly differentiated from normal tissue, and this grade correlates with a less favorable prognosis than grades I and II. Stage I is generally confined within the capsule surrounding one (stage IA) or both (stage IB) ovaries, although in some stage I (i.e. stage IC) cancers, malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. Stage II involves extension or metastasis of the tumor from one or both ovaries to other pelvic structures. In stage IIA, the tumor extends or has metastasized to the uterus, the fallopian tubes, or both. Stage IIB involves extension of the tumor to the pelvis. Stage IIC is stage IIA or IIB in which malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. In stage III, the tumor comprises at least one malignant extension to the small bowel or the omentum, has formed extrapelvic peritoneal implants of microscopic (stage IIIA) or macroscopic (< 2 centimeter diameter, stage IIIB; > 2 centimeter diameter, stage IIIC) size, or has metastasized to a retroperitoneal or inguinal lymph node (an alternate indicator of stage IIIC). In stage IV, distant (i.e. non-peritoneal) metastases of the tumor 20 can be detected.

The durations of the various stages of ovarian cancer are not presently known, but are believed to be at least about a year each (Richart et al., 1969, Am. J. Obstet. Gynecol. 105:386). Prognosis declines with increasing stage designation. For example, 5-year survival rates for patients diagnosed with stage I, II, III, and IV ovarian cancer are 80%, 57%, 25%, and 8%, respectively.

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Despite being the third most prevalent gynecological cancer, ovarian cancer is the leading cause of death among those afflicted with gynecological cancers. The disproportionate mortality of ovarian cancer is attributable to a substantial absence of symptoms among those afflicted with early-stage ovarian cancer and to difficulty diagnosing ovarian cancer at an early stage. Patients afflicted with ovarian cancer most often present with non-specific complaints, such as abnormal vaginal bleeding,

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gastrointestinal symptoms, urinary tract symptoms, lower abdominal pain, and generalized abdominal distension. These patients rarely present with paraneoplastic symptoms or with symptoms which clearly indicate their affliction. Presently, less than about 40% of patients afflicted with ovarian cancer present with stage I or stage II.

Management of ovarian cancer would be significantly enhanced if the disease could be detected at an earlier stage, when treatments are much more generally efficacious.

Ovarian cancer may be diagnosed, in part, by collecting a routine medical history from a patient and by performing physical examination, x-ray examination, and chemical and hematological studies on the patient. Hematological tests which may be indicative of ovarian cancer in a patient include analyses of serum levels of proteins designated CA125 and DF3 and plasma levels of lysophosphatidic acid (LPA). Palpation of the ovaries and ultrasound techniques (particularly including endovaginal ultrasound and color Doppler flow ultrasound techniques) can aid detection of ovarian tumors and differentiation of ovarian cancer from benign ovarian cysts. However, a definitive diagnosis of ovarian cancer typically requires performing exploratory laparotomy of the patient.

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Potential tests for the detection of ovarian cancer (e.g., screening, reflex or monitoring) may be characterized by a number of factors. The "sensitivity" of an assay refers to the probability that the test will yield a positive result in an individual afflicted with ovarian cancer. The "specificity" of an assay refers to the probability that the test will yield a negative result in an individual not afflicted with ovarian cancer. The "positive predictive value" (PPV) of an assay is the ratio of true positive results (i.e. positive assay results for patients afflicted with ovarian cancer) to all positive results (i.e. positive assay results for patients afflicted with ovarian cancer + positive assay results for patients not afflicted with ovarian cancer). It has been estimated that in order for an assay to be an appropriate population-wide screening tool for ovarian cancer the assay must have a PPV of at least about 10% (Rosenthal et al., 1998, Sem. Oncol. 25:315-325). It would thus be desirable for a screening assay for detecting ovarian cancer in patients to have a high sensitivity and a high PPV. Monitoring and reflex tests would also require appropriate specifications.

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Owing to the cost, limited sensitivity, and limited specificity of known methods of detecting ovarian cancer, screening is not presently performed for the general population. In addition, the need to perform laparotomy in order to diagnose ovarian cancer in patients who screen positive for indications of ovarian cancer limits the desirability of population-wide screening, such that a PPV even greater than 10% would be desirable.

Prior use of serum CA125 level as a diagnostic marker for ovarian cancer indicated that this method exhibited insufficient specificity for use as a general screening method. Use of a refined algorithm for interpreting CA125 levels in serial retrospective samples obtained from patients improved the specificity of the method without shifting detection of ovarian cancer to an earlier stage (Skakes, 1995, Cancer 76:2004). Screening for LPA to detect gynecological cancers including ovarian cancer exhibited a sensitivity of about 96% and a specificity of about 89%. However, CA125based screening methods and LPA-based screening methods are hampered by the presence of CA125 and LPA, respectively, in the serum of patients afflicted with conditions other than ovarian cancer. For example, serum CA125 levels are known to be associated with menstruation, pregnancy, gastrointestinal and hepatic conditions such as colitis and cirrhosis, pericarditis, renal disease, and various non-ovarian malignancies. Serum LPA is known, for example, to be affected by the presence of non-ovarian gynecological malignancies. A screening method having a greater specificity for ovarian cancer than the current screening methods for CA125 and LPA could provide a population-wide screening for early stage ovarian cancer.

Presently greater than about 60% of ovarian cancers diagnosed in patients are stage III or stage IV cancers. Treatment at these stages is largely limited to cytoreductive surgery (when feasible) and chemotherapy, both of which aim to slow the spread and development of metastasized tumor. Substantially all late stage ovarian cancer patients currently undergo combination chemotherapy as primary treatment, usually a combination of a platinum compound and a taxane. Median survival for responding patients is about one year. Combination chemotherapy involving agents such as doxorubicin, cyclophosphamide, cisplatin, hexamethylmelamine, paclitaxel, and methotrexate may improve survival rates in these groups, relative to single-agent therapies. Various recently-developed chemotherapeutic agents and treatment regimens

have also demonstrated usefulness for treatment of advanced ovarian cancer. For example, use of the topoisomerase I inhibitor topectan, use of amifostine to minimize chemotherapeutic side effects, and use of intraperitoneal chemotherapy for patients having peritoneally implanted tumors have demonstrated at least limited utility.

Presently, however, the 5-year survival rate for patients afflicted with stage III ovarian cancer is 25%, and the survival rate for patients afflicted with stage IV ovarian cancer is 8%.

In summary, the earlier ovarian cancer is detected, the aggressiveness of therapeutic intervention and the side effects associated with therapeutic intervention are minimized. More importantly, the earlier the cancer is detected, the survival rate and quality of life of ovarian cancer patients is enhanced. Thus, a pressing need exists for methods of detecting ovarian cancer as early as possible. There also exists a need for methods of detecting recurrence of ovarian cancer as well as methods for predicting and monitoring the efficacy of treatment. The present invention satisfies these needs.

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SUMMARY OF THE INVENTION

The invention relates to novel genes associated with ovarian cancer as well as methods of assessing whether a patient is afflicted with ovarian cancer. This method comprises the step of comparing the level of expression of a marker in a patient sample, wherein the marker is listed in Tables 1-2, and the normal level of expression of the marker in a control, e.g., a sample from a patient without ovarian cancer. A significant difference between the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer. Preferably, a protein corresponding to the marker is a secreted protein. Alternatively, the marker can correspond to a protein having an extracellular portion, to one which is normally expressed in ovarian tissue at a detectable level, or both.

In one method, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%. Also preferred are embodiments of the method wherein the marker is over- or under-expressed by at least two-fold in at least about 20% of stage I ovarian cancer patients, stage II ovarian cancer patients, stage III ovarian cancer patients, grade I ovarian cancer patients, grade I ovarian cancer patients, epithelial

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ovarian cancer patients, stromal ovarian cancer patients, germ cell ovarian cancer patients, malignant ovarian cancer patients, benign ovarian patients, serous neoplasm ovarian cancer patients, mucinous neoplasm ovarian cancer patients, endometrioid neoplasm ovarian cancer patients and/or clear cell neoplasm ovarian cancer patients.

In one embodiment of the methods of the present invention, the patient sample is an ovary-associated body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluids, urine, and fluids collected by peritoneal rinsing. In another embodiment, the sample comprises cells obtained from the patient. In this embodiment, the cells may be found in a fluid selected from the group consisting of a fluid collected by peritoneal rinsing, a fluid collected by uterine rinsing, a uterine fluid, a uterine exudate, a pleural fluid, and an ovarian exudate. In another embodiment, the patient sample is *in vivo*.

In accordance with the methods of the present invention, the level of expression of the marker in a sample can be assessed, for example, by detecting the presence in the sample of:

- a protein corresponding to the marker or fragment of the protein (e.g. using a reagent, such as an antibody, an antibody derivative, or an antibody fragment, which binds specifically with the protein)
- a transcribed polynucleotide (e.g. an mRNA or a cDNA), or fragment thereof, having at least a portion with which the marker is substantially homologous (e.g. by contacting a mixture of transcribed polynucleotides obtained from the sample with a substrate having one or more of the markers listed in Tables 1-2 fixed thereto at selected positions)
- a transcribed polynucleotide or fragment thereof, wherein the polynucleotide anneals with the marker under stringent hybridization conditions.
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by a protein corresponding to the marker

The methods of the present invention are particularly useful for patients with an identified pelvic mass or symptoms associated with ovarian cancer. The methods of the present invention can also be of particular use with patients having an enhanced risk of developing ovarian cancer (e.g., patients having a familial history of ovarian cancer,

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patients identified as having a mutant oncogene, and patients at least about 50 years of age). The methods of the present invention may further be of particular use in monitoring the efficacy of treatment of an ovarian cancer patient (e.g. the efficacy of chemotherapy).

The methods of the present invention may be performed using a plurality (e.g. 2, 3, 5, or 10 or more) of markers. According to a method involving a plurality of markers, the level of expression in the sample of each of a plurality of markers independently selected from the markers listed in Tables 1-2 is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with ovarian cancer. The markers of Tables 1-2 may also be used in combination with known ovarian cancer markers in the methods of the present invention.

In a preferred method of assessing whether a patient is afflicted with ovarian cancer (e.g., new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker in a patient sample, wherein at least one marker is selected from the markers of Tables 1-2, and
- b) the normal level of expression of the marker in a control non-ovarian cancer sample.
- A significant difference between the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer.

The methods of the present invention further include a method of assessing the efficacy of a test compound for inhibiting ovarian cancer in a patient. This method comprises comparing:

- a) expression of a marker in a first sample obtained from the patient and maintained in the presence of the test compound, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the test compound.

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A significant difference between the level of expression of the marker in the first sample, relative to the second sample, is an indication that the test compound is efficacious for inhibiting ovarian cancer in the patient. For example, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

The invention further relates to a method of assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient. This method comprises comparing:

- a) expression of a marker in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significant difference between the level of expression of the marker in the second sample, relative to the first sample, is an indication that the therapy is efficacious for inhibiting ovarian cancer in the patient.

It will be appreciated that in these methods the "therapy" may be any traditional therapy for treating ovarian cancer including, but not limited to, chemotherapy, radiation therapy and surgical removal of tissue, e.g., an ovarian tumor. Thus, the methods of the invention may be used to evaluate a patient before, during and after thereapy, for example, to evaluate the reduction in tumor burden.

The present invention therefore further comprises a method for monitoring the progression of ovarian cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker,
 wherein the marker is selected from the group consisting of the markers listed in Tables
 1-2;
 - b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of ovarian cancer in the patient.
- The invention also includes a method of selecting a composition for inhibiting ovarian cancer in a patient. This method comprises the steps of:
 - a) obtaining a sample comprising cancer cells from the patient;

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- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker listed in Tables 1-2 in each of the aliquots; and
- d) selecting one of the test compositions which alters the level of expression of the marker in the aliquot containing that test composition, relative to other test compositions.

In addition, the invention includes a method of inhibiting ovarian cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
 - b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
 - c) comparing expression of a marker listed in Tables 1-2 in each of the aliquots; and
 - d) administering to the patient at least one of the test compositions which alters the level of expression of the marker in the aliquot containing that test composition, relative to other test compositions.

The invention also includes a kit for assessing whether a patient is afflicted with ovarian cancer. This kit comprises reagents for assessing expression of a marker listed in Tables 1-2.

In another aspect, the invention relates to a kit for assessing the suitability of each of a plurality of compounds for inhibiting an ovarian cancer in a patient. The kit comprises a reagent for assessing expression of a marker listed in Tables 1-2, and may also comprise a plurality of compounds.

In another aspect, the invention relates to a kit for assessing the presence of ovarian cancer cells. This kit comprises an antibody, wherein the antibody binds specifically with a protein corresponding to a marker listed in Tables 1-2. The kit may also comprise a plurality of antibodies, wherein the plurality binds specifically with a protein corresponding to a different marker listed in Tables 1-2.

The invention also includes a kit for assessing the presence of ovarian cancer cells, wherein the kit comprises a nucleic acid probe. The probe binds specifically with a transcribed polynucleotide corresponding to a marker listed in Tables 1-2. The kit

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may also comprise a plurality of probes, wherein each of the probes binds specifically with a transcribed polynucleotide corresponding to a different marker listed in Tables 1-2.

The invention further relates to a method of making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with ovarian cancer. The method comprises isolating a protein corresponding to a marker listed in Tables 1-2, immunizing a mammal using the isolated protein, isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for production of an antibody which specifically binds with the protein to isolate the hybridoma. The invention also includes an antibody produced by this method.

The invention further includes a method of assessing the ovarian carcinogenic potential of a test compound. This method comprises the steps of:

- a) maintaining separate aliquots of ovarian cells in the presence and absence of the test compound; and
- b) comparing expression of a marker in each of the aliquots.

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The marker is selected from those listed in Tables 1-2. A significantly altered level of expression of the marker in the aliquot maintained in the presence of (or exposed to) the test compound, relative to the aliquot maintained in the absence of the test compound, is an indication that the test compound possesses ovarian carcinogenic potential.

Additionally, the invention includes a kit for assessing the ovarian carcinogenic potential of a test compound. The kit comprises ovarian cells and a reagent for assessing expression of a marker in each of the aliquots. The marker is selected from those listed in Tables 1-2.

The invention further relates to a method of treating a patient afflicted with ovarian cancer or at risk of developing ovarian cancer. This method comprises enhancing expression of a marker listed in Tables 1-2 or providing to cells of the patient a protein corresponding to a marker listed in Tables 1-2, wherein the marker is underexpressed in patients afflicted with ovarian cancer. The protein can be provided to the cells, for example, by providing a vector comprising a polynucleotide encoding the protein to the cells.

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The invention includes another method of treating a patient afflicted with ovarian cancer or at risk of developing ovarian cancer. This method comprises inhibiting expression or overexpression of a marker listed in Tables 1-2 by, e.g., providing to cells of the patient an antisense oligonucleotide complementary to a polynucleotide corresponding to a marker listed in Tables 1-2, wherein the marker is overexpressed in patients afflicted with ovarian cancer.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known ovarian cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than ovarian cancer.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to newly discovered genes associated with the cancerous state of ovarian cells. It has been discovered that the level of expression of individual genes, also referred to as markers, and combinations of these genes, correlates with the presence of ovarian cancer in a patient. Methods are provided for detecting the presence of ovarian cancer in a sample, the absence of ovarian cancer in a sample, the stage of an ovarian cancer, and with other characteristics of ovarian cancer that are relevant to prevention, diagnosis, characterization, and therapy of ovarian cancer in a patient.

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Definitions

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a naturally-occurring polymer corresponding to at least one of the novel nucleic acids listed in Tables 1-2. For example, markers include, without limitation, sense and anti-sense strands of genomic DNA (*i.e.* including any introns occurring therein), RNA generated by transcription of genomic DNA (*i.e.* prior to splicing), RNA generated by splicing of RNA transcribed from genomic DNA, and proteins generated by translation of spliced RNA (*i.e.* including proteins both before and

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after cleavage of normally cleaved regions such as transmembrane signal sequences). As used herein, "marker" may also include a cDNA made by reverse transcription of an RNA generated by transcription of genomic DNA (including spliced RNA).

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example a marker of the invention. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic monomers.

An "ovary-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through ovarian cells or into which cells or proteins shed from ovarian cells *e.g.*, ovarian epithelium, are capable of passing. Exemplary ovary-associated body fluids include blood fluids, lymph, ascites, gynecological fluids, cystic fluid, urine, and fluids collected by peritoneal rinsing.

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The "normal" level of expression of a marker is the level of expression of the marker in ovarian cells of a patient, e.g. a human, not afflicted with ovarian cancer.

"Over-expression" and "under-expression" of a marker refer to expression of the marker of a patient at a greater or lesser level, respectively, than normal level of expression of the marker (e.g. at least two-fold greater or lesser level).

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

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An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

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A "transcribed polynucleotide" is a polynucleotide (e.g. an RNA, a cDNA, or an analog of one of an RNA or cDNA) which is complementary to or homologous with all or a portion of a mature RNA made by transcription of a genomic DNA corresponding to a marker of the invention and normal post-transcriptional processing (e.g. splicing), if any, of the transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

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"Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. 15

A marker is "fixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (e.g. standard saline citrate, pH 7.4) without a substantial fraction of the marker dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g. encodes a natural protein).

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Expression of a marker in a patient is "significantly" higher or lower than the normal level of expression of a marker if the level of expression of the marker is greater or less, respectively, than the normal level by an amount greater than the standard error of the assay employed to assess expression, and preferably at least twice, and more preferably three, four, five or ten times that amount. Alternately, expression of the marker in the patient can be considered "significantly" higher or lower than the normal level of expression if the level of expression is at least about two, and preferably at least about three, four, or five times, higher or lower, respectively, than the normal level of expression of the marker.

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Ovarian cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, ovarian cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (e.g. a package or container) comprising at least one reagent, e.g. a probe, for specifically detecting a marker of the invention, the manufacture being promoted, distributed, or sold as a unit for performing the methods of the present invention.

Description

The present invention is based, in part, on identification of novel markers which are over-expressed in ovarian cancer cells as compared to their expression in normal (*i.e.* non-cancerous) ovarian cells. The markers of the invention correspond to DNA, RNA, and polypeptide molecules which can be detected in one or both of normal and cancerous ovarian cells. The enhanced expression of one or more of these markers in ovarian cells is herein correlated with the cancerous state of the tissue. The invention thus includes compositions, kits, and methods for assessing the cancerous state of ovarian cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells).

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with ovarian cancer;
- assessing the stage of ovarian cancer in a human patient;
- 3) assessing the grade of ovarian cancer in a patient;
- 4) assessing the benign or malignant nature of ovarian cancer in a patient;
- 25 5) assessing the histological type of neoplasm (e.g. serous, mucinous, endometroid, or clear cell neoplasm) associated with ovarian cancer in a patient;
 - 6) making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with ovarian cancer;
 - 30 7) assessing the presence of ovarian cancer cells;
 - assessing the efficacy of one or more test compounds for inhibiting ovarian cancer in a patient;

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 assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient;

- 10) monitoring the progression of ovarian cancer in a patient;
- 11) selecting a composition or therapy for inhibiting ovarian cancer in a patient;
- 12) treating a patient afflicted with ovarian cancer;
- 13) inhibiting ovarian cancer in a patient;

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- 14) assessing the ovarian carcinogenic potential of a test compound; and
- 10 inhibiting an ovarian cancer in a patient at risk for developing ovarian cancer.

The invention thus includes a method of assessing whether a patient is afflicted with ovarian cancer. This method comprises comparing the level of expression of a marker in a patient sample and the normal level of expression of the marker in a control, e.g., a non-ovarian cancer sample. A significant difference between the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer. The marker is selected from the group consisting of the markers listed in Tables 1-2.

The polynucleotides set forth in Tables 1-2 represent previously unidentified nucleotide sequences. These nucleotide sequences were identified through subtracted library experiments described herein. Also provided by this invention are polynucleotides that correspond to the polynucleotides of Tables 1-2. In one embodiment, these polynucleotides are obtained by identification of a larger fragment or full-length coding sequence of these polynucleotides. Gene delivery vehicles, host cells, compositions and databases (all described herein) containing these polynucleotides are also provided by this invention.

Any marker or combination of markers listed in Tables 1-2, as well as any known markers in combination with the markers set forth in Tables 1-2, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in ovarian cancer cells and the level of expression of the same marker in normal ovarian

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cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater.

It is recognized that certain markers correspond to proteins which are secreted from ovarian cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the protein corresponding to each of these markers can be detected in an ovary-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a protein corresponding to a marker of the invention include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker corresponds to a secreted protein. In order to make this determination, the protein corresponding to a marker is expressed in a test cell (e.g. a cell of an ovarian cell line), extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (e.g. using a labeled antibody which binds specifically with the protein).

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The following is an example of a method which can be used to detect secretion of a protein corresponding to a marker of the invention. About 8 x 10⁵ 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINETM (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain

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methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans- 35 STM reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris. The presence of the protein in the supernatant is an indication that the protein is secreted.

Examples of ovary-associated body fluids include blood fluids (e.g. whole blood, blood serum, blood having platelets removed therefrom, etc.), lymph, ascitic fluids, gynecological fluids (e.g. ovarian, fallopian, and uterine secretions, menses, vaginal douching fluids, fluids used to rinse cervical cell samples, etc.), cystic fluid, urine, and fluids collected by peritoneal rinsing (e.g. fluids applied and collected during laparoscopy or fluids instilled into and withdrawn from the peritoneal cavity of a human patient). In these embodiments, the level of expression of the marker can be assessed by assessing the amount (e.g. absolute amount or concentration) of the marker in an ovary-associated body fluid obtained from a patient. The fluid can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g. storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the fluid.

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Many ovary-associated body fluids (*i.e.* usually excluding urine) can have ovarian cells, *e.g.* ovarian epithelium, therein, particularly when the ovarian cells are cancerous, and, more particularly, when the ovarian cancer is metastasizing. Cell-containing fluids which can contain ovarian cancer cells include, but are not limited to, peritoneal ascites, fluids collected by peritoneal rinsing, fluids collected by uterine rinsing, uterine fluids such as uterine exudate and menses, pleural fluid, and ovarian exudates. Thus, the compositions, kits, and methods of the invention can be used to detect expression of markers corresponding to proteins having at least one portion which is displayed on the surface of cells which express it. Examples of such proteins are indicated in the Tables herein. Although not every protein having at least one cell-surface portion is indicated in the Tables, it is a simple matter for the skilled artisan to determine whether the protein corresponding to any particular marker comprises a cell-surface protein. For example, immunological methods may be used to detect such

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proteins on whole cells, or well known computer-based sequence analysis methods (e.g. the SIGNALP program; Nielsen et al., 1997, Protein Engineering 10:1-6) may be used to predict the presence of at least one extracellular domain (i.e. including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker corresponding to a protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (e.g. using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed molecule or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

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In a preferred embodiment, expression of a marker is assessed using an antibody (e.g. a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (e.g. an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {e.g. biotin-streptavidin}), or an antibody fragment (e.g. a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a protein corresponding to the marker, such as the protein encoded by the open reading frame corresponding to the marker or such a protein which has undergone all or a portion of its normal post-translational modification.

In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a polynucleotide comprising the marker, and fragments thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide

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polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (e.g. at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker of the invention. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (e.g. detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (e.g. a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal ovarian cells and cancerous ovarian cells.

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It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over- or under-expressed in cancers of various types, including specific ovarian cancers, as well as other cancers such as breast cancer, cervical cancer, etc. For example, it will be confirmed that some of the markers of the invention are over- or under-expressed in most (i.e. 50% or more) or substantially all (i.e. 80% or more) of ovarian cancer.

Furthermore, it will be confirmed that certain of the markers of the invention are associated with ovarian cancer of various stages (i.e. stage I, II, III, and IV ovarian cancers, as well as subclassifications IA, IB, IC, IIA, IIB, IIC, IIIA, IIIB, and IIIC, using the FIGO Stage Grouping system for primary carcinoma of the ovary; 1987, Am. J. Obstet. Gynecol. 156:236), of various histologic subtypes (e.g. serous, mucinous, endometroid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma,

cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Müllerian) mixed tumor, mesonephroid tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant ovarian tumors; Scully, Atlas of Tumor Pathology, 3d series, Washington DC), and various grades (i.e. grade I {well differentiated}, grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in patients. In addition, these compositions, kits, and methods can be used to detect and differentiate epithelial, stromal, and germ cell ovarian cancers.

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When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with an ovarian cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a PPV of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 99.5%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (i.e. using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a

significantly enhanced level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. In another embodiment, a significantly lower level of expression in the sample of each of the plurality of markers, relative to the corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. In yet another embodiment, a significantly enhanced level of expression of one or more marks and a significantly lower level of expression of one or more markers in a sample relative to the corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-ovarian origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-epithelial tissue, and more preferably a marker which is normally not expressed in a non-ovarian tissue.

Only a small number of markers are known to be associated with ovarian cancers (e.g. AKT2, Ki-RAS, ERBB2, c-MYC, RB1, and TP53; Lynch, supra). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

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Known oncogenes and tumor suppressor genes include, for example, abl, abr, akt2, apc, bcl2α, bcl3, bcr, brca1, brca2, cbl, ccnd1, cdc42, cdk4, crk-II, csf1r/fms, dbl, dcc, dpc4/smad4, e-cad, e2f1/rbap, egfr/erbb-1, elk1, elk3, eph, erg, ets1, ets2, fer, fgr/src2, fli1/ergb2, fos, fps/fes, fra1, fra2, fyn, hck, hek, her2/erbb-2/neu, her3/erbb-3, her4/erbb-4, hras1, hst2, hstf1, igfbp2, ink4a, ink4b, int2/fgf3, jun, junb, jund, kip2, kit, kras2a, kras2b, lck, lyn, mas, max, mcc, mdm2, met, mlh1, mmp10, mos,

msh2, msh3, msh6, myb, myba, mybb, myc, mycl1, mycn, nf1, nf2, nme2, nras, p53, pdgfb, phb, pim1, pms1, pms2, ptc, pten, raf1, rap1a, rb1, rel, ret, ros1, ski, src1, tal1, tgfbr2, tgfb3, tgfbr3, thra1, thrb, tiam1, timp3, tjp1, tp53, trk, vav, vhl, vil2, waf1, wnt1, wnt2, wt1, and yes1 (Hesketh, 1997, In: The Oncogene and Tumour Suppressor Gene Facts Book, 2nd Ed., Academic Press; Fishel et al., 1994, Science 266:1403-1405).

Known growth factors include platelet-derived growth factor alpha, plateletderived growth factor beta (simian sarcoma viral {v-sis} oncogene homolog), thrombopoietin (myeloproliferative leukemia virus oncogene ligand, megakaryocyte growth and development factor), erythropoietin, B cell growth factor, macrophage stimulating factor 1 (hepatocyte growth factor-like protein), hepatocyte growth factor (hepapoietin A), insulin-like growth factor 1 (somatomedia C), hepatoma-derived growth factor, amphiregulin (schwannoma-derived growth factor), bone morphogenetic proteins 1, 2, 3, 3 beta, and 4, bone morphogenetic protein 7 (osteogenic protein 1), bone morphogenetic protein 8 (osteogenic protein 2), connective tissue growth factor, connective tissue activation peptide 3, epidermal growth factor (EGF), teratocarcinomaderived growth factor 1, endothelin, endothelin 2, endothelin 3, stromal cell-derived factor 1, vascular endothelial growth factor (VEGF), VEGF-B, VEGF-C, placental growth factor (vascular endothelial growth factor-related protein), transforming growth factor alpha, transforming growth factor beta 1 and its precursors, transforming growth factor beta 2 and its precursors, fibroblast growth factor 1 (acidic), fibroblast growth factor 2 (basic), fibroblast growth factor 5 and its precursors, fibroblast growth factor 6 and its precursors, fibroblast growth factor 7 (keratinocyte growth factor), fibroblast growth factor 8 (androgen-induced), fibroblast growth factor 9 (glia-activating factor), pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1), brain-derived neurotrophic factor, and recombinant glial growth factor 2.

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Known proteases include interleukin-1 beta convertase and its precursors, Mch6 and its precursors, Mch2 isoform alpha, Mch4, Cpp32 isoform alpha, Lice2 gamma cysteine protease, Ich-1S, Ich-1L, Ich-2 and its precursors, TY protease, matrix metalloproteinase 1 (interstitial collagenase), matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase), matrix metalloproteinase 7 (matrilysin), matrix metalloproteinase 8 (neutrophil collagenase), matrix metalloproteinase 12 (macrophage elastase), matrix metalloproteinase 13 (collagenase 3), metallopeptidase 1,

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cysteine-rich metalloprotease (disintegrin) and its precursors, subtilisin-like protease Pc8 and its precursors, chymotrypsin, snake venom-like protease, cathepsin l, cathepsin D (lysosomal aspartyl protease), stromelysin, aminopeptidase N, plasminogen, tissue plasminogen activator, plasminogen activator inhibitor type II, and urokinase-type plasminogen activator.

Known protein kinases include DAP kinase, serine/threonine protein kinases NIK, PK428, Krs-2, SAK, and EMK, interferon-inducible double stranded RNA dependent protein kinase, FAST kinase, AIM1, IPL1-like midbody-associated protein kinase-1, NIMA-like protein kinase 1 (NLK1), the cyclin-dependent kinases (cdk1-10), checkpoint kinase Chk1, Nek3 protein kinase, BMK1 beta kinase, Clk1, Clk2, Clk3, extracellular signal-regulated kinases 1, 3, and 6, cdc28 protein kinase 1, cdc28 protein kinase 2, pLK, Myt1, c-Jun N-terminal kinase 2, Cam kinase 1, the MAP kinases, insulin-stimulated protein kinase 1, beta-adrenergic receptor kinase 2, ribosomal protein S6 kinase, kinase suppressor of ras-1 (KSR1), putative serine/threonine protein kinase 15 Prk, PkB kinase, cAMP-dependent protein kinase, cGMP-dependent protein kinase, type II cGMP-dependent protein kinase, protein kinases Dyrk2, Dyrk3, and Dyrk4, Rhoassociated coiled-coil containing protein kinase p160ROCK, protein tyrosine kinase t-Ror1, Ste20-related kinases, cell adhesion kinase beta, protein kinase 3, stress-activated protein kinase 4, protein kinase Zpk, serine kinase hPAK65, dual specificity mitogenactivated protein kinases 1 and 2, casein kinase I gamma 2, p21-activated protein kinase Pak1, lipid-activated protein kinase PRK2, focal adhesion kinase, dual-specificity tyrosine-phosphorylation regulated kinase, myosin light chain kinase, serine kinases SRPK2, TESK1, and VRK2, B lymphocyte serine/threonine protein kinase, stressactivated protein kinases JNK1 and JNK2, phosphorylase kinase, protein tyrosine kinase Tec, Jak2 kinase, protein kinase Ndr, MEK kinase 3, SHB adaptor protein (a Src homology 2 protein), agammaglobulinaemia protein-tyrosine kinase (Atk), protein kinase ATR, guanylate kinase 1, thrombopoeitin receptor and its precursors, DAG kinase epsilon, and kinases encoded by oncogenes or viral oncogenes such as v-fgr (Gardner-Rasheed), v-abl (Abelson murine leukemia viral oncogene homolog 1), v-arg 30 (Abelson murine leukemia viral oncogene homolog, Abelson-related gene), v-fes and vfps (feline sarcoma viral oncogene and Fujinami avian sarcoma viral oncogene homologs), proto-oncogene c-cot, oncogene pim-1, and oncogene mas1.

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It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing ovarian cancer and their medical advisors. Patients recognized as having an enhanced risk of developing ovarian cancer include, for example, patients having a familial history of ovarian cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (i.e. non-cancerous) human ovarian tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of ovarian cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the ovarian cells which is suspected of being cancerous. For example, when laparoscopy or other medical procedure, reveals the presence of a lump on one portion of a patient's ovary, but not on another portion of the same ovary or on the other ovary, the normal level of expression of a marker may be assessed using one or both or the non-affected ovary and a non-affected portion of the affected ovary, and this normal level of expression may be compared with the level of expression of the same marker in an affected portion (i.e. the lump) of the affected ovary. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of ovarian cancer in the patient, from archived patient samples, and the like.

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The invention includes compositions, kits, and methods for assessing the presence of ovarian cancer cells in a sample (e.g. an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the

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kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of ovarian cancer cells (e.g. in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a nucleic acid or polypeptide corresponding to a marker of the invention. Suitable reagents for binding with a polypeptide corresponding to a marker of the invention include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a nucleic acid (e.g. a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (e.g. SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal ovarian cells, a sample of ovarian cancer cells, and the like.

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The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an ovarian cancer. In this method, a protein corresponding to a marker of the invention is isolated (e.g. by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the isolated protein. The vertebrate may optionally (and preferably) be immunized at least one additional time with the isolated protein, so that the vertebrate exhibits a robust immune response to the protein. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this

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manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the protein. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

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The invention also includes a method of assessing the efficacy of a test compound for inhibiting ovarian cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of ovarian cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of ovarian cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an ovarian cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous ovarian cells).

This method thus comprises comparing expression of a marker in a first ovarian cell sample and maintained in the presence of the test compound and expression of the marker in a second ovarian cell sample and maintained in the absence of the test compound. A significant alteration in the level of expression of a marker listed in Tables 1-2 is an indication that the test compound inhibits ovarian cancer. The ovarian cell samples may, for example, be aliquots of a single sample of normal ovarian cells obtained from a patient, pooled samples of normal ovarian cells obtained from a patient, cells of a normal ovarian cell line, aliquots of a single sample of ovarian cancer cells obtained from a patient, pooled samples of ovarian cancer cells obtained from a patient, cells of an ovarian cancer cell line, or the like. In one embodiment, the samples are ovarian cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various ovarian cancers are tested in order to identify the compound which is likely to best inhibit the ovarian cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting ovarian cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the

efficacy of test compounds, if the therapy induces a significant alteration in the level of expression of a marker listed in Tables 1-2 then the therapy is efficacious for inhibiting ovarian cancer. As above, if samples from a selected patient are used in this method, then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting ovarian cancer in the patient.

As described herein, ovarian cancer in patients is associated with an altereration in the level of expression of one or more markers listed in Tables 1-2. While, as discussed above, some of these changes in expression level result from occurrence of the ovarian cancer, others of these changes induce, maintain, and promote the cancerous state of ovarian cancer cells. Thus, ovarian cancer characterized by an increase in the level of expression of one or more markers listed in either or both of Tables 1-2 can be inhibited by inhibiting expression of those markers.

Expression of a marker listed in Tables 1-2 can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the ovarian cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein corresponding to the marker(s). Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of the marker(s). The compound so identified can be provided to the patient in order to inhibit expression of the marker(s) in the ovarian cancer cells of the patient.

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Expression of a marker listed in Tables 1-2 can be enhanced in a number of ways generally known in the art. For example, a polynucleotide encoding the marker and operably linked with an appropriate promoter/regulator region can be provided to ovarian cancer cells of the patient in order to induce enhanced expression of the protein (and mRNA) corresponding to the marker therein. Alternatively, if the protein is capable of crossing the cell membrane, inserting itself in the cell membrane, or is normally a secreted protein, then expression of the protein can be enhanced by providing

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the protein (e.g. directly or by way of the bloodstream or another ovary-associated fluid) to ovarian cancer cells in the patient.

As described above, the cancerous state of human ovarian cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human ovarian cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human ovarian cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significant alteration in the level of expression of a marker listed in Tables 1-2 in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human ovarian cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

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One aspect of the invention pertains to novel isolated nucleic acid molecules that correspond to a marker of the invention, including nucleic acids which encode a polypeptide corresponding to a marker of the invention or a portion of such a polypeptide. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify nucleic acid molecules that correspond to a marker of the invention, including nucleic acids which encode a polypeptide corresponding to a marker of the invention, and fragments of such nucleic acid molecules, e.g., those suitable for use as PCR primers for the amplification or mutation of nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

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An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., ed., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

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In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a nucleic acid corresponding to a marker of the invention or to the nucleotide sequence of a nucleic acid encoding a protein which corresponds to a marker of the invention. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently

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complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker of the invention or which encodes a polypeptide corresponding to a marker of the invention. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which misexpress the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, e.g., detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a protein which corresponds to a marker of the invention, and thus encode the same protein.

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It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (e.g., the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

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As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 15 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid corresponding to a marker of the invention or to a nucleic acid encoding a protein corresponding to a marker of the invention. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 75% (80%, 85%, preferably 90%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions for annealing two single-stranded DNA each of which is at least about 100 bases in length and/or for annealing a single-stranded DNA and a single-stranded RNA each of which is at least about 100 bases in length, are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C. Further preferred hybridization conditions are taught in Lockhart, et al., Nature Biotechnology, Volume 14, 1996 August:1675-1680; Breslauer, et al., Proc. Natl. Acad. Sci. USA, Volume 83, 1986 June: 3746-3750; Van Ness, et al., Nucleic Acids Research, Volume 19, No. 19, 1991 September: 5143-5151; McGraw, et al., BioTechniques,

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Volume 8, No. 6 1990: 674-678; and Milner, *et al.*, Nature Biotechnology, Volume 15, 1997 June: 537-541, all expressly incorporated by reference.

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration. Alternatively, amino acid residues that are conserved among the homologs of various species (e.g., murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from the naturally-occurring proteins which correspond to the markers of the invention, yet retain biological activity. In one embodiment, such a protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of one of the proteins which correspond to the markers of the invention.

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An isolated nucleic acid molecule encoding a variant protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of nucleic acids of the invention, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an

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amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule corresponding to a marker of the invention or complementary to an mRNA sequence corresponding to a marker of the invention. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a noncoding region of the coding strand of a nucleotide sequence encoding a polypeptide of the invention. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

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An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine

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substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a polypeptide corresponding to a selected marker of the invention to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then

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to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α-units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, Nature 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a polypeptide corresponding to a marker of the invention can be designed based upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech et al. U.S. Patent No. 4,987,071; and Cech et al. U.S. Patent No. 5,116,742). Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, e.g., Bartel and Szostak, 1993, Science 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a polypeptide of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the polypeptide (e.g., the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene

(1991) Anticancer Drug Des. 6(6):569-84; Helene (1992) Ann. N.Y. Acad. Sci. 660:27-36; and Maher (1992) Bioassays 14(12):807-15.

In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al., 1996, Bioorganic & Medicinal Chemistry 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), supra; Perry-O'Keefe et al. (1996) Proc. Natl. Acad. Sci. USA 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup (1996), supra; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, supra; Perry-O'Keefe et al., 1996, Proc. Natl. Acad. Sci. USA 93:14670-675).

In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNASE H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup,

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1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-11124).

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In other embodiments, the oligonucleotide can include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad.

Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, e.g., PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, Bio/Techniques 6:958-976) or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with

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one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

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One aspect of the invention pertains to isolated proteins which correspond to individual markers of the invention, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a polypeptide corresponding to a marker of the invention. In one embodiment, the native polypeptide corresponding to a marker can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, polypeptides corresponding to a marker of the invention are produced by recombinant DNA techniques. Alternative to recombinant expression, a polypeptide corresponding to a marker of the invention can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical. precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

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Biologically active portions of a polypeptide corresponding to a marker of the invention include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the protein corresponding to the marker, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding protein. A biologically active portion of a protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of a polypeptide of the invention.

Preferred polypeptides are encoded by the nucleotide sequences of Tables 1-2. Other useful proteins are substantially identical (e.g., at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the protein of the corresponding naturally-occurring protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

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To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions (e.g., overlapping positions) $\times 100$). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an

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algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) Nucleic Acids Res. 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) CABIOS 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a k-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins corresponding to a marker of the invention. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a polypeptide corresponding to a marker of the invention operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the polypeptide corresponding to the marker). Within the fusion protein, the term "operably linked" is intended to indicate that the polypeptide of the invention and the heterologous polypeptide are fused in-frame to each

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other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the polypeptide of the invention.

One useful fusion protein is a GST fusion protein in which a polypeptide corresponding to a marker of the invention is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a polypeptide corresponding to a marker of the invention can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al., supra) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a polypeptide corresponding to a marker of the invention is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a polypeptide of the invention. Inhibition of ligand/receptor interaction can be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g. promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a polypeptide of the invention in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of receptors with ligands.

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Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, e.g., Ausubel et al., supra). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of the secreted protein or other proteins of interest. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to the described polypeptides having a signal sequence, as well as to polypeptides from which the signal sequence has been proteolytically cleaved (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a protein which is ordinarily not secreted or is otherwise difficult to isolate. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

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The present invention also pertains to variants of the polypeptides corresponding to individual markers of the invention. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally

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occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a protein of the invention which function as either agonists 10 (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the polypeptides of the invention from a degenerate oligonucleotide sequence. Methods for 20 synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, 1983, Tetrahedron 39:3; Itakura et al., 1984, Annu. Rev. Biochem. 53:323; Itakura et al., 1984, Science 198:1056; Ike et al., 1983 Nucleic Acid Res. 11:477).

In addition, libraries of fragments of the coding sequence of a polypeptide corresponding to a marker of the invention can be used to generate a variegated population of polypeptides for screening and subsequent selection of variants. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be

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derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

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Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327-331).

An isolated polypeptide corresponding to a marker of the invention, or a fragment thereof, can be used as an immunogen to generate antibodies using standard techniques for polyclonal and monoclonal antibody preparation. The full-length polypeptide or protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the polypeptides of the invention, and encompasses an epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with a marker of the invention to which the protein corresponds. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, e.g., hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized polypeptide. The preparation can

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further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent.

Accordingly, another aspect of the invention pertains to antibodies directed against a polypeptide of the invention. The terms "antibody" and "antibody substance" as used interchangeably herein refer to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds an antigen, such as a polypeptide of the invention, e.g., an epitope of a polypeptide of the invention. A molecule which specifically binds to a given polypeptide of the invention is a molecule which binds the polypeptide, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope.

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Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be harvested or isolated from the subject (e.g., from the blood or serum of the subject) and further

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purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected or (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) Nature 256:495-497, the human B cell hybridoma technique (see Kozbor et al., 1983, Immunol. Today 4:72), the EBV-hybridoma technique (see Cole et al., pp. 77-96 In Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally Current Protocols in Immunology, Coligan et al. ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an

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antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) Bio/Technology 9:1370-1372; Hay et al. (1992) Hum. Antibod. Hybridomas 3:81-85; Huse et al. (1989) Science 246:1275-1281; Griffiths et al. (1993) EMBO J. 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) Science 240:1041-1043; Liu et al. (1987) Proc. Natl. Acad. Sci. USA 84:3439-3443; Liu et al. (1987) J. Immunol. 139:3521-3526; Sun et al. (1987) Proc. Natl. Acad. Sci. USA 84:214-218; Nishimura et al. (1987) Cancer Res. 47:999-1005; Wood et al. (1985) Nature 314:446-

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449; and Shaw et al. (1988) J. Natl. Cancer Inst. 80:1553-1559); Morrison (1985) Science 229:1202-1207; Oi et al. (1986) Bio/Techniques 4:214; U.S. Patent 5,225,539; Jones et al. (1986) Nature 321:552-525; Verhoeyan et al. (1988) Science 239:1534; and Beidler et al. (1988) J. Immunol. 141:4053-4060.

Antibodies of the invention may be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an ovarian cancer. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) Int. Rev. Immunol. 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers et al., 1994, Bio/technology 12:899-903).

An antibody directed against a polypeptide corresponding to a marker of the invention (e.g., a monoclonal antibody) can be used to isolate the polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation.

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Moreover, such an antibody can be used to detect the marker (e.g., in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (e.g. in an ovary-associated body fluid) as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ¹²⁵I, ¹³¹I, ³⁵S or ³H.

Further, an antibody (or fragment thereof) can be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

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The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

Accordingly, in one aspect, the invention provides substantially purified antibodies or fragments thereof, and non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequences of the present invention, an amino acid sequence encoded by the cDNA of the present invention, a fragment of at least 15 amino acid residues of an amino acid sequence of the present invention, an amino acid sequence which is at least 95% identical to the amino acid sequence of the present invention (wherein the percent identity is determined using the

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ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4) and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of the nucleic acid molecules of the present invention, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. In various embodiments, the substantially purified antibodies of the invention, or fragments thereof, can be human, non-human, chimeric and/or humanized antibodies.

In another aspect, the invention provides non-human antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of: the amino acid sequence of the present invention, an amino acid sequence encoded by the cDNA of the present invention, a fragment of at least 15 amino acid residues of the amino acid sequence of the present invention, an amino acid sequence which is at least 95% identical to the amino acid sequence of the present invention (wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4) and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of the nucleic acid molecules of the present invention, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the nonhuman antibodies of the invention can be polyclonal antibodies or monoclonal antibodies.

In still a further aspect, the invention provides monoclonal antibodies or fragments thereof, which antibodies or fragments specifically bind to a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequences of the present invention, an amino acid sequence encoded by the cDNA of the present invention, a fragment of at least 15 amino acid residues of an amino acid sequence of the present invention, an amino acid sequence which is at least 95% identical to an amino acid sequence of the present invention (wherein the percent

identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4) and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of the nucleic acid molecules of the present invention, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The substantially purified antibodies or fragments thereof may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a polypeptide of the invention. In a particularly preferred embodiment, the substantially purified antibodies or fragments thereof, the non-human antibodies or fragments thereof, and/or the monoclonal antibodies or fragments thereof, of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of the present invention.

Any of the antibodies of the invention can be conjugated to a therapeutic moiety or to a detectable substance. Non-limiting examples of detectable substances that can be conjugated to the antibodies of the invention are an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

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The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical composition contains an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

Still another aspect of the invention is a method of making an antibody that specifically recognizes a polypeptide of the present invention, the method comprising immunizing a mammal with a polypeptide. The polypeptide used as an immungen comprises an amino acid sequence selected from the group consisting of the amino acid sequence of the present invention, an amino acid sequence encoded by the cDNA of the nucleic acid molecules of the present invention, a fragment of at least 15 amino acid residues of the amino acid sequence of the present invention, an amino acid sequence

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which is at least 95% identical to the amino acid sequence of the present invention (wherein the percent identity is determined using the ALIGN program of the GCG software package with a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4) and an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of the nucleic acid molecules of the present invention, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C.

After immunization, a sample is collected from the mammal that contains an antibody that specifically recognizes the polypeptide. Preferably, the polypeptide is recombinantly produced using a non-human host cell. Optionally, the antibodies can be further purified from the sample using techniques well known to those of skill in the art. The method can further comprise producing a monoclonal antibody- producing cell from the cells of the mammal. Optionally, antibodies are collected from the antibody-producing cell.

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III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a polypeptide corresponding to a marker of the invention (or a portion of such a polypeptide). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g.,

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replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, Methods in Enzymology: Gene Expression Technology vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

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The recombinant expression vectors of the invention can be designed for

25 expression of a polypeptide corresponding to a marker of the invention in prokaryotic

(e.g., E. coli) or eukaryotic cells (e.g., insect cells {using baculovirus expression

vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in

Goeddel, supra. Alternatively, the recombinant expression vector can be transcribed

and translated in vitro, for example using T7 promoter regulatory sequences and T7

30 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

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One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of

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nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al., 1983, Mol. Cell Biol. 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, Virology 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

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In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al., 1987, Genes Dev. 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, Adv. Immunol. 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, EMBO J. 8:729-733) and immunoglobulins (Banerji et al., 1983, Cell 33:729-740; Queen and Baltimore, 1983, Cell 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, Proc. Natl. Acad. Sci. USA 86:5473-5477), pancreas-specific promoters (Edlund et al., 1985, Science 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-

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regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, *Science* 249:374-379) and the α-fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a

DNA molecule of the invention cloned into the expression vector in an antisense
orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a
manner which allows for expression (by transcription of the DNA molecule) of an RNA
molecule which is antisense to the mRNA encoding a polypeptide of the invention.

Regulatory sequences operably linked to a nucleic acid cloned in the antisense
orientation can be chosen which direct the continuous expression of the antisense RNA
molecule in a variety of cell types, for instance viral promoters and/or enhancers, or
regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type
specific expression of antisense RNA. The antisense expression vector can be in the
form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic
acids are produced under the control of a high efficiency regulatory region, the activity
of which can be determined by the cell type into which the vector is introduced. For a
discussion of the regulation of gene expression using antisense genes see Weintraub et
al., 1986, Trends in Genetics, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant

20 expression vector of the invention has been introduced. The terms "host cell" and

"recombinant host cell" are used interchangeably herein. It is understood that such

terms refer not only to the particular subject cell but to the progeny or potential progeny

of such a cell. Because certain modifications may occur in succeeding generations due

to either mutation or environmental influences, such progeny may not, in fact, be

25 identical to the parent cell, but are still included within the scope of the term as used

herein.

A host cell can be any prokaryotic (e.g., E. coli) or eukaryotic cell (e.g., insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via

conventional transformation or transfection techniques. As used herein, the terms
"transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium

phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a polypeptide corresponding to a marker of the invention. Accordingly, the invention further provides methods for producing a polypeptide corresponding to a marker of the invention using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the marker is produced. In another embodiment, the method further comprises isolating the marker polypeptide from the medium or the host cell.

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The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a polypeptide corresponding to a marker of the invention have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a polypeptide corresponding to a marker of the invention sequences have been altered. Such animals are useful for studying the function and/or activity of the polypeptide corresponding to the marker and for identifying and/or evaluating modulators of polypeptide activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more

preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a polypeptide corresponding to a marker of the invention into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a polypeptide corresponding to a marker of the invention into which a deletion, addition or substitution has been introduced to

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thereby alter, e.g., functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi, 1987, Cell 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, e.g., Li et al., 1992, Cell 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see, e.g., Bradley, Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline 25 transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) Current Opinion in Bio/Technology 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso et al. (1992) Proc.

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Natl. Acad. Sci. USA 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of Saccharomyces cerevisiae (O'Gorman et al., 1991, Science 251:1351-1355). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be
produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") corresponding to a marker of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a polypeptide or nucleic acid corresponding to a marker of the invention. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid corresponding to a marker of the invention. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically

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acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid corresponding to a marker of the invention and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, e.g., Zuckermann et al., 1994, J. Med. Chem. 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, Anticancer Drug Des. 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994). J. Med. Chem. 37:2678; Cho et al. (1993) Science 261:1303; Carrell et al. (1994) Angew. Chem.

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Int. Ed. Engl. 33:2059; Carell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2061; and in Gallop et al. (1994) J. Med. Chem. 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten, 1992, Biotechniques 13:412-421), or on beads (Lam, 1991, Nature 354:82-84), chips (Fodor, 1993, Nature 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull et al, 1992, Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith, 1990, Science 249:386-390; Devlin, 1990, Science 249:404-406; Cwirla et al, 1990, Proc. Natl. Acad. Sci. 87:6378-6382; Felici, 1991, J. Mol. Biol. 222:301-310; Ladner, supra.).

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In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a marker can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ¹²⁵I, ³⁵S, ¹⁴C, or ³H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the activity of a marker or a biologically active portion thereof. In all likelihood, the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker "substrate".

One necessary embodiment of the invention in order to facilitate such screening

is the use of the marker to identify its natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay

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(see, e.g., U.S. Patent No. 5,283,317; Zervos et al, 1993, Cell 72:223-232; Madura et al, 1993, J. Biol. Chem. 268:12046-12054; Bartel et al, 1993, Biotechniques 14:920-924; Iwabuchi et al, 1993 Oncogene 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker or downstream elements of a marker-mediated signaling pathway. Alternatively, such marker binding partners may also be found to be inhibitors of the marker.

The two-hybrid system is based on the modular nature of most transcription

factors, which consist of separable DNA-binding and activation domains. Briefly, the
assay utilizes two different DNA constructs. In one construct, the gene that encodes a
marker protein fused to a gene encoding the DNA binding domain of a known
transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a
library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is

fused to a gene that codes for the activation domain of the known transcription factor. If
the "bait" and the "prey" proteins are able to interact, in vivo, forming a markerdependent complex, the DNA-binding and activation domains of the transcription factor
are brought into close proximity. This proximity allows transcription of a reporter gene
(e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to
the transcription factor. Expression of the reporter gene can be readily detected and cell
colonies containing the functional transcription factor can be isolated and used to obtain
the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (e.g., affect either positively or negatively) interactions between a marker and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an ovarian cancer marker identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

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The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker and its binding partner involves preparing a reaction mixture containing the marker and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker and its binding partner.

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The assay for compounds that interfere with the interaction of the marker with its binding partner may be conducted in a heterogeneous or homogeneous format.

Heterogeneous assays involve anchoring either the marker or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the markers and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, e.g., compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

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In a heterogeneous assay system, either the marker or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-Stransferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (e.g., physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described 20 above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker or a marker binding partner can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxysuccinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

30 In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing)

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and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

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In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993 Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from

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the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, 1998, J Mol. Recognit. 11:141-148; Hage and Tweed, 1997, J. Chromatogr. B. Biomed. Sci. Appl., 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolycis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker and its binding partner.

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Also within the scope of the present invention are methods for direct detection of interactions between the marker and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, e.g., Lakowicz et al, U.S. Patent No. 5,631,169; Stavrianopoulos et al, U.S. Patent No. 30 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (e.g., marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (e.g.,

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marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA or protein, corresponding to a marker in the cell, is determined. The level of expression of mRNA or protein in the presence of the candidate compound is compared to the level of expression of mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

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In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a

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marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., an marker modulating agent, an antisense marker nucleic acid molecule, an marker-specific antibody, or an marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (e.g. a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or

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researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

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Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance

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of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

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Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

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For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound

and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (e.g., into the ovarian epithelium). A method for lipidation of antibodies is described by Cruikshank et al. (1997) J. Acquired Immune Deficiency Syndromes and Human Retrovirology 14:193.

The nucleic acid molecules corresponding to a marker of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, e.g., Chen et al., 1994, Proc. Natl. Acad. Sci. USA 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g. retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

25 V. Predictive Medicine

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The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of polypeptides or nucleic acids corresponding to one or more markers of the invention, in order to determine whether an individual is at risk of developing ovarian cancer. Such assays can be used for

prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit ovarian cancer or to treat or prevent any other disorder {i.e. in order to understand any ovarian carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

10 A. Diagnostic Assays

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An exemplary method for detecting the presence or absence of a polypeptide or nucleic acid corresponding to a marker of the invention in a biological sample involves obtaining a biological sample (e.g. an ovary-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of a polypeptide corresponding to a marker of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of a polypeptide corresponding to a marker of the invention include introducing into a subject a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

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For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

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Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polypthylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

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It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz et al., U.S. Patent No. 5,631,169; Stavrianopoulos, et al., U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter).

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In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, e.g., Sjolander, S. and Urbaniczky, C., 1991, Anal. Chem. 63:2338-2345 and Szabo et al., 1995, Curr. Opin. Struct. Biol. 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In

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differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7).

Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, N.H., 1998, J. Mol. Recognit. Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. J Chromatogr B Biomed Sci Appl 1997 Oct 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate

complexed assay components from unbound components (see, e.g., Ausubel et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of mRNA corresponding to the marker can
be determined both by *in situ* and by *in vitro* formats in a biological sample using
methods known in the art. The term "biological sample" is intended to include tissues,
cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues,
cells and fluids present within a subject. Many expression detection methods use
isolated RNA. For *in vitro* methods, any RNA isolation technique that does not select
against the isolation of mRNA can be utilized for the purification of RNA from ovarian
cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley
& Sons, New York 1987-1999). Additionally, large numbers of tissue samples can

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readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

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An alternative method for determining the level of mRNA corresponding to a marker of the present invention in a sample involves the process of nucleic acid amplification, e.g., by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, Proc. Natl. Acad. Sci. USA, 88:189-193), self sustained sequence replication (Guatelli et al., 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al., 1988, Bio/Technology 6:1197), rolling circle replication (Lizardi et al., U.S. Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if

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such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the ovarian cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, e.g., a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, e.g., a non-ovarian cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

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Preferably, the samples used in the baseline determination will be from ovarian cancer or from non-ovarian cancer cells of ovarian tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is ovarian specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from ovarian cells provides a means for grading the severity of the ovarian cancer state.

In another embodiment of the present invention, a polypeptide corresponding to a marker is detected. A preferred agent for detecting a polypeptide of the invention is an antibody capable of binding to a polypeptide corresponding to a marker of the invention, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

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Proteins from ovarian cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether ovarian cells express a marker of the present invention.

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In one format, antibodies, or antibody fragments, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from ovarian cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

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The invention also encompasses kits for detecting the presence of a polypeptide or nucleic acid corresponding to a marker of the invention in a biological sample (e.g. an ovary-associated body fluid such as a urine sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing ovarian cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a polypeptide or an mRNA encoding a polypeptide corresponding to a marker of the invention in a biological sample and means for determining the amount of the polypeptide or mRNA in the sample (e.g., an antibody which binds the polypeptide or an oligonucleotide probe which binds to DNA or mRNA encoding the polypeptide). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a polypeptide corresponding to a marker of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide corresponding to a marker of the invention or (2)

a pair of primers useful for amplifying a nucleic acid molecule corresponding to a marker of the invention. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

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Agents or modulators which have a stimulatory or inhibitory effect on expression of a marker of the invention can be administered to individuals to treat (prophylactically or therapeutically) ovarian cancer in the patient. In conjunction with such treatment, the pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.*, drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens.

Accordingly, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Linder (1997) Clin. Chem. 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate

dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. 10 These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard 15 doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of 20 ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

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Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening,

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but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for ovarian cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent can be desirable to increase expression of the marker(s) to higher levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent can be desirable to decrease expression of the marker(s) to lower levels than detected, i.e., to decrease the effectiveness of the agent.

D. Electronic Apparatus Readable Media and Arrays

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Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the

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present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

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A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the nucleic acid sequence corresponding to the markers can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of dataprocessor structuring formats (e.g., text file or database) may be employed in order to obtain or create a medium having recorded thereon the the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer and/or recommending a particular treatment for ovarian cancer or pre-ovarian cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has ovarian cancer or a predisposition to ovarian cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer, and/or recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

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The present invention also provides a business method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes

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can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression per se and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

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In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of ovarian cancer, progression of ovarian cancer, and processes, such a cellular transformation associated with ovarian cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, ovarian cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (e.g., with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (e.g., early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (e.g., an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate markers in the art include: Koomen et al. (2000) J. Mass. Spectrom. 35: 258-264; and James (1994) AIDS Treatment News Archive 209.

used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a

25 pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection

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of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda et al. US 6,033,862; Hattis et al. (1991) Env. Health Perspect. 90: 229-238; Schentag (1999) Am. J. Health-Syst. Pharm. 56 Suppl. 3: S21-S24; and Nicolau (1999) Am. J. Health-Syst. Pharm. 56 Suppl. 3: S16-S20.

The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker which correlates with a specific clinical drug response or susceptibility in a subject (see, e.g., McLeod et al. (1999) Eur. J. Cancer 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker is related to the predicted response of the subject to a specific drug or class of drugs prior to administration of the drug. By assessing the presence or quantity of one or more pharmacogenomic markers in a subject, a drug therapy which is most appropriate for the subject, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein for specific tumor markers in a subject, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be present in the subject. Similarly, the presence or absence of a specific sequence mutation in marker DNA may correlate with drug response. The use of pharmacogenomic markers therefore permits the application of the most appropriate treatment for each subject without having to administer the therapy.

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VI. Experimental Protocol

A. Subtracted Libraries

Subtracted libraries are generated using a PCR based method that allows the isolation of clones expressed at higher levels in one population of mRNA (tester) compared to another population (driver). Both tester and driver mRNA populations are converted into cDNA by reverse transcription, and then PCR amplified using the SMART PCR kit from Clontech. Tester and driver cDNAs are then hybridized using the PCR-Select cDNA subtraction kit from Clontech. This technique results in both subtraction and normalization, which is an equalization of copy number of low-abundance and high-abundance sequences. After generation of the subtractive libraries, a group of 96 or more clones from each library is tested to confirm differential expression by reverse Southern hybridization.

To create the subtracted libraries, a first group of regular cDNA libraries was constructed. Library johOa was constructed from a pool of 5 normal ovarian epithelial cell cultures. Library johOb was constructed from a pool of 5 ascites short cultured samples from ovarian cancer patients. Library johOc was constructed from a pool of 6 serous late stage (III/IV) tumor samples. Three subtracted libraries were generated from tumor samples. Library johOd was a subtracted ascites library, where the tester was johOb, and the driver was johOa. The johOe and the johOf library were both subtracted stage III/IV serous tumor libraries. The tester for both of these libraries was johOc, and the driver was a pooled RNA from normal tissues. The tissues used for this driver pool were: kidney, small intestine, prostate, lung, heart, muscle, spleen, pancreas, liver, and lymphocyte. Library cMhOg was the same as the johOc and johOf libraries, with the exception that normal ovary was added to the driver. cMhOh, i, j, and k are all stage I/II subtracted libraries made from pooled tumor RNAs of different histological types (h=serous, I-endometriod, j=clear cell, k=mucinous). The driver was the same for these 4 libraries. It consisted of normal ovarian epithelial RNA and PBML RNA. Of the markers listed in Table 1, SEQ ID NOS: 1-129, 916-1029, 1566-1571 and 1607-1865 were identified in library johOa. Markers identified in johOb include SEQ ID NOS: 130-177, 1030-1081, 1572-1574, and 1866-1974. Markers identified in johOc include SEQ ID NOS: 178-269, 1082-1120, 1575-1577, and 1975-2060. Markers identified in johOd include SEQ ID NOS: 270-370, 1121-1304, 1578-1592, and 2061-2244. Markers

identified in johOe include SEQ ID NOS: 371-611, 1305-1416, 1593-1596 and 2245-2487. Markers identified in johOf include SEQ ID NOS: 612-915, 1417-1565, 1597-1606, and 2488-2871. Of the markers listed in Table 1A, SEQ ID NOS: 2872-2976, 3817-3898, 4438-4443 and 4474-4675 were identified in library cMhOg. Markers identified in cMhOh include SEQ ID NOS: 2977-3376, 3899-4072, 4444-4455, and 4676-5303. Markers identified in cMhOi include SEQ ID NOS: 3377-3495, 4073-4158, 4456-4460, and 5304-5637. Markers identified in cMhOj include SEQ ID NOS: 3496-3742, 4195-4390, 4461-4468, and 5638-6197. Markers identified in cMhOk include SEQ ID NOS: 3743-3816, 4391-4437, 4469-4473 and 6198-6398.

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VII. Summary Of The Data Provided In The Tables

Tables 1, 1A, 2 and 3 are being filed concurrently herewith on a compact disc in lieu of paper copies. The compact disc submitted is formatted from an IBM-PC and is compatible with MS-Windows. The disc contains the following four (4) files:

Table1.text, containing 1,223kb, Table1A.text, containing 1,582kb, Table2.text, containing 10,600kb, and Table3.text, containing 568kb. The material on the compact disc, namely Tables 1, 1A, 2 and 3, is expressly incorporated by reference.

Tables 1 and 1A show 6398 novel nucleotide sequences. These 6398 novel sequences were determined to be novel through various BLAST searches of available databases. Of these novel markers, SEQ ID NOS: 1566 – 1606 and 4438-4473 are preferred, SEQ ID NOS: 916-1565 and 3817-4437 are more preferred, and SEQ ID NOS: 1 – 915 and 2872-3816 are most preferred.

The sequences of Tables 1 and 1A were re-interpreted and vector sequences removed and those sequences are set forth in Table 2.

Table 3 correlates the SEQ ID NOS. from Tables 1 and 1A with those of Table 2.

The contents of all references, patents, published patent applications, and databases cited throughout this application are hereby incorporated by reference.

30 Other Embodiments

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention

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described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

Claims

- 1. An isolated nucleic acid molecule comprising a nucleotide sequence of Tables 1-2, or a complement thereof.
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- 2. A vector which contains the nucleic acid molecule of claim 1.
- 3. A host cell which contains the nucleic acid molecule of claim 1.
- 4. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence of Tables 1-2.
 - 5. An antibody which selectively binds to a polypeptide of claim 4.
- 6. A method for producing a polypeptide comprising culturing the host cell of claim 3 under conditions in which the nucleic acid molecule is expressed.
 - 7. A method for detecting the presence of a polypeptide of claim 4 in a sample comprising:
- a) contacting the sample with a compound which selectively binds to the polypeptide; and
 - b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a polypeptide of claim 4 in the sample.
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- 8. A kit comprising a compound which selectively binds to the polypeptide of claim 4.

- 9. A method for detecting the presence of a nucleic acid molecule of claim 1 in a sample comprising:
 - a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and
- b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a nucleic acid molecule of claim 1 in the sample.
- 10. The method of claim 9, wherein the sample comprises mRNA molecules10 and is contacted with a nucleic acid probe.
 - 11. The method of claim 9, wherein the sample is isolated from ovarian tissue.
- 15 12. The method of claim 9, wherein the sample is a tumor sample.
 - 13. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1.
- 20 14. A method of assessing whether a patient is afflicted with ovarian cancer, the method comprising comparing:
 - a) the level of expression of a marker in a patient sample, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) the normal level of expression of the marker in a control nonovarian cancer sample,

wherein a significant difference between the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer.

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15. The method of claim 14, wherein the marker corresponds to a secreted protein.

- 16. The method of claim 14, wherein the marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.
- 17. The method of claim 14, wherein the sample comprises cells obtained 5 from the patient.
 - 18. The method of claim 17, wherein the sample is an ovarian tissue sample.
- 19. The method of claim 14, wherein the sample is an ovary-associated body 10 fluid.
 - 20. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a protein or protein fragment corresponding to the marker.

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- 21. The method of claim 20, wherein the presence of the protein or protein fragment is detected using a reagent which specifically binds with the protein or protein fragment.
- 20 22. The method of claim 21, wherein the reagent is selected from the group consisting of an antibody, an antibody derivative, and an antibody fragment.
 - 23. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a transcribed polynucleotide or portion thereof, wherein the transcribed polynucleotide comprises the marker.
 - 24. The method of claim 23, wherein the transcribed polynucleotide is an mRNA.

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25. The method of claim 23, wherein the transcribed polynucleotide is a cDNA.

- 26. The method of claim 23, wherein the step of detecting further comprises amplifying the transcribed polynucleotide.
- 27. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a transcribed polynucleotide which anneals with the marker or anneals with a portion of a polynucleotide wherein the polynucleotide comprises the marker, under stringent hybridization conditions.
- 10 28. The method of claim 14, wherein the level of expression of the marker in the sample differs from the normal level of expression of the marker in a patient not afflicted with ovarian cancer by a factor of at least about 2.
- 29. The method of claim 14, wherein the level of expression of the marker in the sample differs from the normal level of expression of the marker in a patient not afflicted with ovarian cancer by a factor of at least about 5.
 - 30. The method of claim 14, comprising comparing:
 - a) the level of expression in the sample of each of a plurality of markers independently selected from the markers listed in Tables 1-2, and
 - b) the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with ovarian cancer.
- wherein the level of expression of more than one of the markers is significantly altered, relative to the corresponding normal levels of expression of the markers, is an indication that the patient is afflicted with ovarian cancer.
- 31. The method of claim 30, wherein the level of expression of each of the markers is significantly altered, relative to the corresponding normal levels of
 30 expression of the markers, is an indication that the patient is afflicted with ovarian cancer.

- 32. The method of claim 30, wherein the plurality comprises at least three of the markers.
- 33. The method of claim 30, wherein the plurality comprises at least five of the markers.
 - 34. A method for monitoring the progression of ovarian cancer in a patient, the method comprising:
- a) detecting in a patient sample at a first point in time, the expression of a marker, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2;
 - b) repeating step a) at a subsequent point in time; and
 - c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of ovarian cancer.

35. The method of claim 34, wherein the marker corresponds to a secreted protein.

- 36. The method of claim 34, wherein the marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.
 - 37. The method of claim 34, wherein the sample comprises cells obtained from the patient.
- 25 38. The method of claim 37, wherein the patient sample is an ovarian tissue sample.
 - 39. The method of claim 34, wherein between the first point in time and the subsequent point in time, the patient has undergone surgery to remove ovarian tissue.

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- 40. A method of assessing the efficacy of a test compound for inhibiting ovarian cancer in a patient, the method comprising comparing:
 - a) expression of a marker in a first sample obtained from the patient and exposed to the test compound, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) expression of the marker in a second sample obtained from the patient, wherein the sample is not exposed to the test compound, wherein a significantly lower level of expression of the marker in the first sample, relative to the second sample, is an indication that the test compound is efficacious for inhibiting ovarian cancer in the patient.
- 41. The method of claim 40, wherein the first and second samples are portions of a single sample obtained from the patient.
- 15 42. The method of claim 40, wherein the first and second samples are portions of pooled samples obtained from the patient.
 - 43. A method of assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient, the method comprising comparing:
- a) expression of a marker in the first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy,

wherein a significantly lower level of expression of the marker in the second sample, relative to the first sample, is an indication that the therapy is efficacious for inhibiting ovarian cancer in the patient.

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- 44. A method of selecting a composition for inhibiting ovarian cancer in a patient, the method comprising:
 - a) obtaining a sample comprising cancer cells from the patient;
 - b) separately exposing aliquots of the sample in the presence of a plurality of test compositions;
 - c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2; and
- d) selecting one of the test compositions which alters the level of
 expression of the marker in the aliquot containing that test composition, relative
 to other test compositions.
 - 45. A method of inhibiting ovarian cancer in a patient, the method comprising:
 - a) obtaining a sample comprising cancer cells from the patient;
 - b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
 - c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2; and
 - d) administering to the patient at least one of the test compositions which alters the level of expression of the marker in the aliquot containing that test composition, relative to other test compositions.
- 25 46. A kit for assessing whether a patient is afflicted with ovarian cancer, the kit comprising reagents for assessing expression of a marker selected from the group consisting of the markers listed in Tables 1-2.
- 47. A kit for assessing the presence of ovarian cancer cells, the kit comprising a nucleic acid probe wherein the probe specifically binds with a transcribed polynucleotide corresponding to a marker selected from the group consisting of the markers listed in Tables 1-2.

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markers listed in Tables 1-2.

- 48. A kit for assessing the suitability of each of a plurality of compounds for inhibiting ovarian cancer in a patient, the kit comprising:
 - a) the plurality of compounds; and
- a reagent for assessing expression of a marker selected from the
 group consisting of the markers listed in Tables 1-2.
 - 49. A method of making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with ovarian cancer, the method comprising:
- isolating a protein or protein fragment corresponding to a marker selected from the group consisting of the markers listed in Tables 1-2;

immunizing a mammal using the isolated protein or protein fragment; isolating splenocytes from the immunized mammal;

fusing the isolated splenocytes with an immortalized cell line to form hybridomas; and

screening individual hybridomas for production of an antibody which specifically binds with the protein or protein fragment to isolate the hybridoma.

50. An antibody produced by a hybridoma made by the method of claim 42.

51. A kit for assessing the presence of human ovarian cancer cells, the kit comprising an antibody, wherein the antibody specifically binds with a protein or protein fragment corresponding to a marker selected from the group consisting of the

- 52. A method of assessing the ovarian cell carcinogenic potential of a test compound, the method comprising:
 - a) maintaining separate aliquots of ovarian cells in the presence and absence of the test compound; and
- b) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2,

wherein a significantly altered level of expression of the marker in the aliquot maintained in the presence of the test compound, relative to the aliquot maintained in the absence of the test compound, is an indication that the test compound possesses human ovarian cell carcinogenic potential.

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53. A kit for assessing the ovarian cell carcinogenic potential of a test compound, the kit comprising ovarian cells and a reagent for assessing expression of a marker, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2.

- 54. A method of inhibiting ovarian cancer in a patient at risk for developing ovarian cancer, the method comprising inhibiting expression of a gene corresponding to a marker selected from the markers listed in Tables 1-2.
- 55. A method of treating a patient afflicted with ovarian cancer, the method comprising providing to cells of the patient an antisense oligonucleotide complementary to a polynucleotide corresponding to a marker selected from the markers listed in Tables 1-2.
- 20 56. A method of inhibiting ovarian cancer in a patient at risk for developing ovarian cancer, the method comprising decreasing expression of a gene corresponding to a marker selected from the markers listed in Tables 1-2.
- 57. A method for determining whether ovarian cancer has metastasized in a 25 patient, the method comprising comparing:
 - a) the level of expression of a marker in a patient smaple, wherein the marker is selected from the group consisting of the markers listed in Tables 1-2, and
- b) the normal level or non-metastatic level of expression of the
 30 marker in a control sample

wherein a significant difference betweent he level of expression in the patient sample and the normal level or non-metastatic level is an indication that the ovarian cancer has mestastasized.

- 5 58. The method of claim 57, wherein the marker corresponds to a secreted protein.
 - 59. The method of claim 57, wherein the marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.
 - 60. The method of claim 57, wherein the sample comprises cells obtained from the patient.

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- 61. The method of claim 60, wherein the patient sample is an ovarian tissue sample.
 - 62. A method for assessing the aggressiveness or indolence of ovarian cancer comprising comparing:
 - a) the level of expression of a marker in a sample, wherein at least one marker is selected from the markers of Tables 1-2, and
 - b) the normal level of expression of the marker in a control sample, wherein a significant difference between the level of expression in the sample and the normal level is an indication that the cancer is aggressive or indolent.
- 25 63. The method of claim 62, wherein the marker corresponds to a secreted protein.
 - 64. The method of claim 62, wherein marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.
 - 65. The method of claim 62, wherein the sample comprises cells obtained from the patient.

66. The method of claim 65, wherein the patient sample is an ovarian tissue sample.

TABLE 11/467

Sequence 1

Sequence 2

CGTCCGGAAAGCTGGTGGGAATGCTAAGTTCCGAGAGTTCCTGGAGTCTCAGGAGGATTA
CGATCCTTGCTGGTCCTTGCAGGAGAAGTACAACAGCAGAGCCGCGGCCCTCTTTAGGGA
TAAGGTGGTCGCTCTGGCCGAAGGCAGAGAGTGGTCTTTGGAGTCATCACCTGCCCAGAA
CTGGACCCTACCTNAGCCCANGACGCTGCCGTCCATGGTGCACCGAGTCTCTGGCCAGCC
GCAGAGTGTGACCGCCTCCTNGGACAAGGCTTTTGAAGACTGGCTGAATGATCACCTCGG
CTCCTATCAAGGGGCCCAGGGGAATCGCTACGTGGGGTTTGGGAACACGCCACCGCCTCA
NAAGAAAGAAGATGACTTTCTCAACAACGCCATGTCCTCCCTGTACTCGGGCTGGA
Sequence 3

Sequence 4

Sequence 5

Sequence 6

CGTCCGCGTCCTCGCGGAAAGTTGGGGCAACCTGTTGCTAGTCTGGTCGTTGGTGAC
AGCGAGGCTTCCGCGCTGCTGGTGAGCAGCCCCGGCGTGCCCCGCGGGCTGGAAGA
GGCGGCGGGGTGATGCGGCCCGTGGACGCCCCGCGCCCGCGCCCGCGAGAACCTGGCCTC
CCTGGAGCGCGAGAGCGCCCCGGGCGCCCCGAGAAGCTGCTGGAGATCCA

TABLE 1 2/467

GAGCCTGCTCGACGCCATCAAGAGTGAGGTGGAGGCAGAGGAGCGGGGCGCCCCGGGCCCC AGCACCCGCCCCGCGTGCGGAGGCTGAGGAGNCGGGTGGCTCGGCTGTGCGCCCGAAGC AGAGAGGAAGGCTGCGGAAGCGGCGCGGGTGGGGCAGGCGGGATCGTGGGAGCTGCACNN ACCGGATCGCCGGCTTGCGAGTGCTGAGCCGGCGAGGCCCNCGGGTCTGGAAGCGGA ANCGCGCGGG

Sequence 7

CTGGGGGCTGACAGTCGGCAAAGTTTGGCCCGAAGAGGAAGTGGTCTCAAACCCCGGCAG CGGACGGAGAAACAACTCCAAAGTTGGCGAAAGGCACCGCCCCTACTCCCGGGCTTGCC GCCGCCTCCCGCCCCAGCCCTGGCATCCAGAGTACGGGTCGAGCCCGGGCCATGGAGC CCCCTGGGGAAGGCGCACCAGGGGAGCCTTGGGCGCCCNGGGCTTCGGCCGCGACCCC ATTTGGGGTAGACCACAAGAAGCTTCGGGACCCTTTCGGCACCTTTGGACAGCCAAGAA TGGCTGNTGGGCACCCTTTCTTCT

Sequence 8

GACAATGCAAAGGTGTTGGATTAAAAAAAAAATCTGGTAGTAGAGGGAAATTATGGAGGA TTTTTAAAAAGGTTAATGATAATATCCATCTACTTATGTAACTTTTTTTGGAGATACCTG ATAATAGTGTAGAGTGCATTGGAGAGGAAAAGTAGGAGTTGTAAAGACCATTTTGGATAA ACTTTGAAGCAAGGGATAATGGCCTCAACCAAGGTAGTGGTGCTGAAGATTGTTTACATA AATAAGCAGATACAAATAGAAGGGATTTTTCAAGTGGCATTGTAACTGCACTTTTCAAAG TCAAGGGCTTTCTTAAAATTTTGTTGAAAGCCAAGGAA

Sequence 9

CGCCTTCCCGGGAAGTTTGGAGGGCCCCGNAGGGGAAGCCCCCGCGNCTTCNGGGGGCCN GNCGGGCTTGGAAGGCAANCCCCACCCCAAGTTTCCCCGCCNANGGANTNCAATGAANCT TGACCGGGGCCCCCGGAACCCCNCGCTNGNCTTNTTNGGGGGTGGTTCCTTGGGTTCCG GCCTTTCAAGTTCTTNCCTTTCCCCGGNTTGAAAGAAGGNAAAAGGCCGGGAANGGAAAC CNGGGNAAAACCCGCNGGGNNGGGGCGGCCTTCNNCCGCCNGGGCGCCCCTTGCCNGGG GGGGGNAAAGGGGNCAAAGTTTTCCCNGGGGCCCCCGGGGCCCCGGCNGCCCTTTNAAN TCAAGGGGCCGGGNNCGGNCTTTCCCCAANNCGGCCAAGTTCCTTCAAAGGGGCCCCCC CGGGNTTTGGGCCCGGNCCGGGNCNGNAACCTTGGGGAAGAAAAATTCAAAAAGTTTT NCCTTGGGGGCCCCTTCTTTGCCCCCNTTTAAAGGGAANGGGCNAAAACCTTTNCCCAAC CGNCCAANNGCCCCGTNAAAAAANGGGCCGGCCTTNNTTTTGNCCGGGGCCCCNAANAA TTTTTGGCTTTTAAAGGGGGG

Sequence 10

NCGCGTCCGCCGCATTGTGGCCAAGTGCCATGAGGAGCAGCTGGATCATTCTGTCCAGTC *ATATATTAAGTTCGTGTTCAAGACCAGGGCATGCAAGGAGAGGACTGTACATGAGGAACT GNCTAAAAATGTGACTGGTCTTTTGAAATCAAATGACTCAACAACAGTAAAGCATGTCCT ·CACAAATAAAATCCAGCTTCCCCGGCCTCAGAGATTTCCTGAATCTTACCAAAATGAATT GGACAATCTTGNCATGGTCCTATCCGACCATGTGATTTGGGAAATACAAGGATGCACTTG AAGAAACANGAAGGGCAAACCACAGCGTTGCCAGATTTCTCAAGCGCTGCTTTAC Sequence 11

CGCCNCGCGTCCGGCTTCCTAGAAGAGCACAGTCCCTTAAAGCACCCTCTATTGCTACAA TTAAAAGTCTAGCAGATTGTAACTTTAGTTACACAAGTTCTAGAGATGCTTTTGGCTATG

TABLE 1 3/467

TGGCATCTCCAGCAAAAGATGTGCTATTTACTGATACCATCACCATGAAGGCCAACAGTT
TTGAGTCCAGATTAACACCAAGCAGGTTCATGAAAGCCTTAAGTTATGCATCATTAGATA
AAGAAGATTTATTGAGTCCTATTAATCAAAATACCCTGCAACCGATCTTCCTCAGTGCGG
GCCATGGNGTCCAGTGCCACATNGGGGGGGTCAGAATGATTACATTGGGCTTGCTCTCCC
GGNGGATATAAATGATATATTTCANGGTAAGGGTATTTCTTATTTTTAGACAAAAAACAT
CCCCNCATGATGATCCAGGNGCCAGAGCATTTGCCCTGAATGCAGGAGGGCTTTCATNTG
GNACTGGGNGGGGCTTTGNAAAAAATTTTTT

Sequence 12

Sequence 13

Sequence 14

Sequence 16

NGCCCCGCGTCCGTTTTAATTATTTTGTTNGAGCCTGCANAGTAANGTTNTTAAAAATA
TAACGTTCATACGCATTTTAATTAACTTTGAAAGTTCATATGCATCAGAAAATTTATGAA
AATTTGAATGAAAAAAAATTTCATCTATTTATTTTTCTAATTTTAATGGCAAATTTACACT
ATTATGGCTGATAATTCTGTGAACTTACCTTCTTGTTGACTGATTCTTTTTCCCTTAATC

TABLE 14/467

CCAGCTTTAAGGAGATAGGTGAAGTTATTGTACAAAGTTAAGTGATACCATAAAGTATAT ATTATAAAGTCATACATGGCTTTTGGACAGTNTTATATTTCAGTTGCAGTGCTGCATTCC ATTAAATTTCATAAAATGCTAGGGAAAATGTGTTTGATAAAATTTTNTGCAGTGAGAAAT GACAGACTGAGTGCCTGACAATTTAAGCCACATATGAAAGTATGCAAGTAAAAGANTTCAG GTCCTTAATGTCATCATGTATAAAAAG

Sequence 17

CCACGCGTCCGGACGAGACCAGCCCACTAGTGTCCCCCGAGCGGGCCCAACCCCCGGACT ACACCTTCCCGTCGGGCTCGGGCGCTCACTTTCCGCAGGTGCCCGGGGCGCGGTCCGAG TGGCTGGCGGCCGGCCCGGGCCCCTNTCCGCCGGGCCCGGGCCACCGCCGACCGCTGA GCGGCAGCCACTGTTGGATCGGGCCCGGGGCGCGGNGGCCCAGGGCCAGACCCAAACCGT GGCGGCGCAGGCCCAGGCTCTGGCCGTTCANGCCGNGGCGGCAGTCCACGCCGATCAGGC CCACCGNGAGCGGAACGAG

Sequence 18

Sequence 19

NATGTNGNNCNAAAAAGGCCNGCNTTANAGGCCAGGAAACNCGTAAAAAGGGCNCGCGTT
GCTGTGCGTCTTTTCCATAGGCTCGCGNCCCCCTGACCNAGTCATCAAAAAATCCGA
CNGCTCAAGTCATGAGGTTGGCCGAAAACTCCGACAGGGACTTNTAANAGNATACCCANG
GGCGNTTTCCCCTGGGAAGGCTCCCTTCGTGGCGCNTCTCNNTGTTTCCAGACCCCTGC
CCCGCTTTACNCGGNATTACCCTNGTCCCCGCCNTTTTCTTCCCTTTCGNGGAAAGCGGT
NGGGCGCCTTCTCNTCAATTAGGCTTCACCGCCTGNTAANGGTATTCTCAAGTTNCGGNT
GTANGGGTGCCGTTTTCGCTTCCAAAGNCTGGGGCCCTTNTGTGCCACCGGAAACCCCCCC

Sequence 20

Sequence 21

Sequence 22

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Sequence 23

CGCGTCCGGCTGGGCGAATNAGGGATTCCGGTTCACAATGGATGCTGATAAAGAGAAAGA
TTTGCAGAAATTTCTTAAAAATGTGGATGAAATCTCCAATTTAATTCAGGAGATGAATTC
TGATGACCCAGTTGTGCAACAGAAAGCTGTCCTGGAGACAGAAAAGAGACTACTGCTTAT
GGAGGAAGACCAGGAGGAGGATGAATGCAGGACCACCTTGAACAAGACTATGATCAGTCC
TCCACAAACTGCTCTGAAGAGTGCAGAAGAAATAAACTCAGAGGCCTTCTTGGCATCTGT
GGAGAAGGATGCAAAGGAACGAGCCAAGAGAAGAAGGAAAAAAAGTCTTGGCGGATGC
CCTAAAAGAAAAAGGGAATGAAGCATTTGCTGAAGGCAATTATGAAACAGCTATCCTGCG
CTACAGTGAGGGGTTTGGAGAAAGCTGAAAGGACATGAAAGTGCTGTACACCAACCGAGCCC
AGGCTTATATGAAACTTGAGGA

Sequence 24

GGGAGTCGACCNCGCGTCCGCTCCCTCTGAGTTGCGCTGGGCTTGGCTGCACCATGA
CCCTGGAGGCGATCCGCTACTCGCGGGGCTCCCTGCAGATCCTAGACCAGCTGCTGC
CCAAGCAGAGCCGCTACGAGGCGGTGGGCTCCCTGCAGCCTGGGAGGCCATCCGCG
CCATGAAGGTGCGGGGCCCCGGGCCATAGCCCTGGTGGGCTGTCTCAGCCTCGCCGTGG
AGCTGCAGGCGGCGCCGGGGACCCGGGACTCGCCGCGCCTCGTGGCCTTCCTGCGCGACA
AGCTGAGCTTCCTCGTCACCGCCCGGCCCACCGCTGTCAACATGGCCCGCGCCCCCGCG
ACCTGGCTTGATGTTGCAGCCCGGGAGGCCGAACGGGAGGGGGCGCTACGGAAGAGGCCGG
TCCGGGAGAGAGAGTGATCTGCTGCACCGAGGACATGCTGGAGAAAGACCTCAGAGACAACC
GAAGCATTG

Sequence 25

Sequence 26

Sequence 27

NCCNCGCGTCCGGCCGCGCCCCCCGGGCCGGGCTGTAGCGGGGCCGCGGCTGGACGTGTGCGCCGGGCAGGCGGGCAGGCGGGCAGGCGGGCAGGCGGGGCGGGCGGGCGGGCGGGCGGGCGGGCGGGCCTCCAACGAGGCCACATCAACGGTGCCCTGGAGCCCTCCAACATAGACACCAGCATCCTGGAGGAGGAGTACATCAGCAAGGAGGAGGATGCCTCCGACCTCACACTGCCGGACTCTCCCCC

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AGACTCGGGCTCCGAGGCCTACTCCCCCCAGCAGGTGAATGAGCCCCACCTNCTGCGCACGATAACCCCTGAGACACTGTGCCACGTGGGGAGTGCCCTTC

Sequence 28

CGCGTCCGCNAGGGAGGCCGAGCCAGGCAGGCAACCGGGCAGCAGGCATGATGCCCT CGCCTAGTGACTCCAGCCGCTCGCTGACCAGCCGGCCCAGCACCAGGGGCCTTACCCACC TNCGCCTNCACCGACCCTGGCTGCAGGCCCTGCTTACGCTGGGGCTGGTCCAAGTGCTCC TGGGCATACTGGTGGTCACCTTCAGCATGGTGGCCTCTTCCGTCACCACCACCGAGAGCA TNAAGAGGTCCTGCCCGTCTTGGG

Sequence 29

Sequence 30

Sequence 32

NCGTCCGGGAAACTGGTTCNGATGGTGTCTCCCCAGGAGCGCCTGACACGCACCTTCACA CGCAGCAGCCACACCTACACCCGCACGGAGCGCACGGAGATCAGCAAGACGCGGGGCGGG GAGACAAAGCGCGAGGTGCGGGTGGAGGAGTCCACCCAGGTCGGCGGGGACCCCTTCCCT GCTGTGTTTGGGGACTTCCTGGGCCGGGAGCGCCTGGGATCCTTCGGCAGCATCACCCGG CAGCAGGAGGGTGAGGCCAGCTCTCAGGACATGACTGCACAGGTGACCAGCCCATCGGGC AAGGTGGAAGCCGCAGAGATCGTNGAGGGCGAGGACAGCGCCTACAGCGTGCCCTTTGTG CCCCAGGAAATGGGGCCCCATACGGTCGCTGTCAAGTACCGTGGCCNGCACGTGCCCGGC AGCCCCTTTCAGTTTACTGTGGGGCCGCTNGGTNGAAAGGTGGTGCCCACAAGGTGCGGG CCCGGAGGCAC

Sequence 33

CCGCGTCCGCAGGAAATTGTTAAAAATAATTTGGGGGTGTTTATTGGGGAAGGAAACAGG GCCTTGACAGTGGAGGACTTGGAAGACATGTAATTTAAGATATAGAGTATGATTGTTGGA AAATAAGCATGGAGATCCAGAAGGAATCTTAAGAGTTTTTCTATGCAAGTGAAGATGGAA GAAAATATGTATTTTACAAAAGATAAATTACAAGTACCTTATTTGCTTTGCAAAATAACT TATCATGTTCTTCCACTATTTTTATTATATTTTAATTTTAATGAAACTTATATAACATTT

TABLE 1 7/467

ACACTAAATTTTAAATACATGGCTCAAGACAAAAAAATGGGGGAAAATATTTTTTAAAAAA TCACCCCAAATCCTGGTACTCAGACATAACCACTATTCAAACTTGGCAGAGTAATATTTT TCCTGTCTGCATGTGTGCCACNATGTGTGCATGCATACCACAAAGTAGATGTTTTACTAT ATCTCCTGGGTTATTATCTGCTTTTTTCCC

Sequence 34

Sequence 35

CCCCGCGTCCGGTAGATTGCTTGTGGCTGGCAGTGAAGATGGTGGAGTTCAACTTTTTGA
TATAAGTGGGAGGCTCCCCTCAGGCAGTTTGAAGGCCATACAAAGTAAGAGACAGTTGG
TTTCTGTGTGTTCTGGTTTTATTTTGTTGTAAGCTCTTTTTTTCTCTGGACTTTGGTTAA
AAAGATAGAGATCAGTTTTATGGAGATTATTTGCCTATAGGTACTATATTTCCTGATTGT
TCTAAGAGTGCTTAACTTGGGTTCCGTGGTCCAGTTTCATGGGGCTTATGAATTCCCTAG
AATTGTATGTGATATTTTAGGAAATACACGTTTATCTAGGGAGCTACTCTGTAGCTTTTG
GTTAACTTTAGTGGGGTCTGTGGCCCAGCTGAGATTATGAATTACTGACCTGAAGACAAC
CTTACAGCTGGTAATGACAGCTCTATAGGCCTGTACTGTCTTAGAGGCTCTTATGTTGAA
GTCAAGTANGAAGGTGGATTTTCTTCTTGAATTATAGTGTTTTGCCCCTTTAATAA
Sequence 36

Sequence 37

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Sequence 40

Sequence 42

Sequence 43

Sequence 44

CGTCCGCGAGACTCCCGCGCCCACCACCCCCGGCGGAGCTGCTGATCTGAGCCACTCAATCTGAGCCTGGCTACTAATAAAGTTCGTTTAAAAATCATAATCATTCTTAAGAGAGCGAAAG

TABLE 1 9/467

Sequence 45

Sequence 46

Sequence 47

Sequence 48

TABLE 1 10/467

CTTCGTATAAGTCCCAAAGAACTCAGGCTTATAGCACTAAGCAAATTACCAGTGGGAGGA GGAGGACCTGCCACGGAGCTGGATAATTACATTTAAATATTTTTGCCANTCTGTTGGAGA C

Sequence 50

Sequence 51

Sequence 52

GTCGACCNCGCGTCCGGAAAAAAAAAAAATGACCCAGAGATATTAACAACTTGACCTGGTTA
TACAGTTAGATATTTGCACAGTCTGGACTCCAAACTGGAGGCTTCTGACTCCTCATCTAGG
CTCCTCTCACTCTGCCATTGCATGGGTTTTCTCCATATACCTTCTCCATAAGGTTTTCAC
AAATTTGTCACCGTCAAATAATTATCAAAATTATTCACACTATTATAGATGAAAAATAATG
TGCTTATAAAGATTAAGTAACTTTCCTGAGGGCGCAGGTATCTGGTTCACATAACAACTA
GCCTGGCTTAGAATAAACACATATTTCCTGGTTCTGAAGTTGGTGCCTTCCTACCACTT
TCTGCTGTCTCCTAAAGATAAAGAATGTTATTGGCTCACTGAATTAATCCATTCTGTTCC
TGGCTGAAATAAAAAATTGGTATATTCCTTACGTGAAGTGCAACAGGAAGGGGGCTTTTA
CAACTTCCTTT

Sequence 53

Sequence 55

TABLE 1 11/467

ACCNCGCGTCCGGACCTGTTGGCGACATGGTGGCACCCGTGCTGGAGACTTCTCACGTGT
TTTGCTGCCCAAACCGGGTGCGGGGAGTCCTGAACTGGAGCTCTGGGCCCAGAGGACTTC
TGGCCTTTGGCACGTCCTGCTCCGTGGTGCTCTATGACCCCCTGAAAAGGGTTGTTGTTA
CCAACTTGAATGGTCACACCGCCCGAGTCAATTGCATACAGTGGATTTGTAAACAGGATG
GCTCCCCTTCTACTGAATTAGTTTCTGGAGGATCTGATAATCAAGTGATTCACTGGGAAA
TAGAGGATAATCAGCTTTTAAAAGCAGTGCATCTTCAAGGCCATGAAGGACCTGTTTATG
CGGTGCATGCTGTTTACCAGAGGAGGACATCAAGATCCTGCATTATGTACACTGATCGTT
TCTGCAGCTGCAGATTCTGCTGTTCGACTCTGGTCTAAAAAGGGTCCAGAAAGTAATGTG
CCTTCAAACTTTAAACTTTGGAA

Sequence 57

Sequence 58

Sequence 59

Sequence 60

CGCGTCCGGTGGGAAGCCAGAAGATAAAACCAAATGGCTGGGCACGTCTTTAGGTTATTC
CTAGCTAAGAGTTAAGAGTTGTAAGCTCTCCATTCTTTGTTCTTCAGCCTTAAACTATC
TTTCCTTCTATTAACTTTATTTGTCTCAGTTACAATGATAGAGGTAACTTCACATACTAA
AAGAAATTAGGTTACCATGTGAAACATTCTTCTTGGCTTGTGCTAATGTTATCAGATCCA
AACAGCATCTGAAAGAAAATTTTCCAAGTACGATGTTGTTCTCTTGTTTTTCTGAAATACA

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TATCATATGTTAAAGTGAGAGTTTTTATACATGTTGAAAGAAGTTGAATGACAAA TAGTTACTGAGGCCTCCATTTTCTTACTTCACAGTTAAAATTCCTGTTTCTCTTTGGGTA TAGGAGGGTAGAAAGAAGTGGGAGAGTAATAGCATTTTAAAACACAGAATCAAAAATCAT ATTAAAAGTAG

Sequence 61

Sequence 62

Sequence 63

CCCACTGTAATAGGGGCCTCATCAATGCCCCATGCTCACTGAATAAAGCACTGCCAGCGA AAGGTGAAAAGAGGAACAAAGAACATTNTCCTGGACGCCACCCACAGAAAGCCACNTGCA GGCTTGGCCCTCACCTTGGGGACCTTGGACACGGAGCTGGTTATGTCACATCTGGCTCTC AGAGCTGGGGCAGCTGTCTAGGAGGCCTGATGTAGAAAGCACTCAGCTAAGCCCTATTTA CCGGCACACGGGCACCAGCGCCCCCTNTCAGCAAACTCCACGTNTTATGAAATTAGCACT GGATTTCCACTTCAATTGGA

Sequence 64

Sequence 65

TABLE 1 13/467

Sequence 66

Sequence 69

ACCCANACCTGGGAGGAATTAATGGAATGCTTGNCCCTGGGCAGCCTTAGAAACAGACCC NAGCTTATCTAANGCTGCTCCGAGGCAGTGACCCAACTANGGCTCAGGAAGTCAAGAANA TTGACCAAGCTTATAGTGATCACCTCTTGACCTTTGTGTCACAGTCNTTTTTGCTTTTTAA AACCCTTTTGTGAACCGNTTATGGCCTTTGATTCTGACAGGCATCNTAGTTGTGAAGGGG AACANGGGCAGGATATAATGTTTCGTTTACCAAATACAANAAATCNGANGTACCCAGNT AGATCACAANATTTTTTGGGAGAAGGNCTNTTGGGTCTCTTCCAGGAGNTCACTTCANNN TTGGNAACTTGACAGGGGCTTGGGGGAATTTANTATTCCCCTTTGGGCGCAGGGNCNCAAAN GGGTGGCANTTTCCCTCCTTGGAGNTTTTTTTTTCAAGAANTCCTTGCNTNGGGGAAAGA TGGTTACNANNATCCCGGAATTTCCAACCCCCTTCCCTATTTTTTTTGGTTTAAGG Sequence 70

TABLE 1 14/467

TGTCTCTCCCAGTGCATCCCAGTGCTGTCTCTGCCCCCTGCTGCTTCTGTAAAGATTT
TCTGACACAAGTAACTGCCTCATAGACCTTCCTTTTTATGAAATCCTGAGTTTTGGTTTG
GGTACGTCCTTTTTAGAT

Sequence 71

Sequence 72

CGCCCGCGTCCGGGCGGCTGGTGGGCGACCGGGCGCATCCTCATTGCATGTGCGGCGGC
CCTACCTCGGCCTGACCCCGGCGGCGCCCTGCCCGCCCCTCCAGCATCATGG
CCAGCCCAAGAACCAGGAAGGTTCTTAAAGAAGTCAGGGTGCAGGATGAGAACAACGTTT
GTTTTGAGTGTGGCGCGTTCAATCCTCAGTGGGTCAGTGTGACCTACGGCATCTGGATCT
GCCTGGAGTGCTCGGGGAGACACCGCGGGCTTGGGGTTCACCTCAGCTTTGTGCGCTCTG
TTACTATGGACAAGTGGAAGGACATTGAGCTTGAGAAGATGAAAGCTGGTGGGAATGCTA
AGTTCCGAGAGTTCCTGGAGTCTCAGGAGGATTACCGATCCTTGCTGGTCCTTTGCAGGG
AGAAGTA

Sequence 73

Sequence 74

Sequence 75

CCCGCGTCCGGGCTGGCATGGCTCTATATAAGATTGTTGCANAAANTCCCTACTACTTTT
GGTCTGTGATGAGCTTAATTATGCAATCTATATNGGCACAGGATGAAAACCTCTCAAAAA
CAATGTTTCTGCCCCTTGCTGAGAGAATGGTCGAAAAAATGGTGAAAGAGGACAAGATAG
AAGCTGAGGCTGAAGTTGAACTTTATTATATGATCCTGGAACGTTTGGGAAAGTACCAGG
AGGCCTTGGATGTCATCAGAGGGAAATTAGGAGAGAAGTTGACAAGTGAGATTCACAGTC
GGGAAAATAAATGCATGGCTATNTACAANAAGCTGAGCAGGTGGCCAGAGTGCAATGCCC
TTTNCCGGCGCCCTCTTACT

Sequence 76

GNTGGAGGAGCTTTGCTACTCTGCTCTTTGGCATGACTCCAGGATTTTTTTCTGGAATCC
AACCTCTGTCCTCTTAGGAGAAGGAACCTGTCCTTGGTTCAGATGGCTGGGCATGAGGAG
GAAAATTTCCATTAGTGTAGAAAAGTGCTGGACAGAATCCGGTTTGGAAAATTACAAATC
CAGTTGGTCAAAATAGGCCATTTCCTATGTGTGACCTATTCGTGGTATGCCAACTGGACT
GCTTCCTAAACAGGACGAGGAAAGTGAGGAATATTTTTATATGAAAGCCTTAGCCTGTCT
GGCACCCATGAAAAAAACTATTTATGCACTCCTACTTTCACCCGTCTTTTTTGCATTCTCT

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Sequence 77

GGAGAGTGCCTTGCCGGACCCTCAGGACGAGCTGCTGGGCTGCTACAGTGACCAGGACT
TTCTGGCCAAGCTGCACTGTGTGCGGCAGGCCTTCGAGGGGCTTCTGGAAGACAAGAGTA
ACCAGCTTTTCTTCGGGAAAGTGGGCCGACAGATGGTGACCAGGCCTGATGACCAAGGCTG
AGAAGAGCCCCAAAGGCTTCCTGGAGAGCTACGAGGAGATGCTGAGCTATGCCCTGCGGC
CCGAGACCTGGGCCACAACACGGCTGGAGCTGGAGGCCGAGGGGTGGTATGCATGAGCT
TCTTCGACATCGTGCTGGACTTCATCCTCATGGACGCCTTCGAGGACCTGGAGAACCCTC
CGGCCTCGGTGCTTGCCGTCCTGCGGAACCGCTGGCTGTCANACAGCTTCAAGGAGACCG
CCTTGGCCACTGCTTGCTGGTCGTCCTGAAAG

Sequence 78

Sequence 79

CGCGTCCGCAAGAAGATAACCCCAAACTCTTTTCTCAGAGAGTTTGTAGCCTAGTTTGGG
ATAGATAAGATCCACATATTTAGTCATATAAGACTACAGGAGAGTAGAATAGATGCACCA
GATGGTGTCGAATGAAAGTGGTACTTTGTAGACTATAAGTGCTGTAAATTCTAAAGGACA
GGTTACTTTTGCCTGGAGTGGTCAAGAAAGATTTATTTAAAATAAGGATTTGACGGGCA
GACTTAGCAGTCAAAAGGGAGAAAGCGGGTAAAACAAATGTAAGCCATCATAAGAGTGCA
TGTGGTTTGGAAGCATCAGGGAAAAGACTAGCCAACCTGAAGTAAAAGGTTCGTGCAAAT
TGGGCAATCAATAGCATTAAGTTGGAAACAGCTTGGGGACACACATAAGAGGGCCAGA
GTGTGAATAATTTCATCTAATACTTTATAGCACTTGGACATTTACAGAGCACTTTTCTC
Sequence 80

Sequence 81

CACGCGTCCGCAAAATAGCCCCACATCCNGGCAAAAGGGGCCTTTCCCTTGGCCCAGAAG
AAAAAGGAACAAGTGGAGTGCAGAAGAAAATCTGTACTGAGAGACTTGGGCCTAGCTTGT
CTTCCAGTGAGCCAACCAAGGCTGGTGCTGTCCCATCCAGTCCCTCGACGCCAGCACCAC
CCAGCGCCAAACTTGCCGAGGACTCAGCTCTGCAGGGTGTGCCCTCTCTGGTGGCAGGTG
GAAGTCCACAGACTCTTCAGCCGGTATCCAGCAGTCACGTGGCTAAAGCTCCCAGTCTGA
CCTTCGCTTCCCCGCCAGTCCTGTCTGCGCATCAGACACCTCTCCATGGGTTAGAGA
GCAACTCTCCCCTTTCACCACTGTCCGCTAATTATAGCTCACCTTTATGGGCTGCAGAGC
ACCTCTGCCGCAGCCCAGATATCTTTTCAGAGCAGCAGAGCAAACATAGGCGCTTTC
AGAATACCCTAGTAGTCCTACATAAAATCTGGGTTGCTGGAGATCACTTTTGAAAACCAA

G



Sequence 84

GTCCGCCGCTTCCGGTCTCCCCGGGCCGGCGCTGGCCTGACTGCGGCCCCGGTCCG
TAGCACTCCGCCCTCCGCTTCTCCCGCCCTGTAGCCGCAAGACTGCTTCAGCCTTTCCC
TGTGCTGCCCCTGCCGCGCGATGGAGACGAGCTCGAGCTGCGAGAGTCTTGGCTCCCAGC
CGGCGGCGCTCGGCCCCCAGCGTGGACTCCTTGTCCAGTTAATGTGTTAAGAGCCATT
GACATTTGAAGATCATCAGAAGTGAAGATAAAACATCTCAAAAATTATAATTGCCTCCAC
TTCTCATTCAGAGAATTCAGTGCATACAAAATCAGCTTCTGTTGTATCATCAGATTCCAT
TTCAACTTCTGCCGACAACTTTTCTCCTGATTTGAGGCCCATGCAGTCCAGTTCGGGAGC
TAAGT

Sequence 85

Sequence 86

Sequence 87

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NACAAGTTGCANGGGTCACAAAAACATCGTGAATTTTGATNGGAGTGGTTACAATCCAC Sequence 88

CGTCCGTTTAATTATAACCTAGATTGTCTGGGCAACGGCAGGAACGGAGTGCCACTGTGG
AGCAGATAACTGCAGTGGTTTTCTAGGAGTGCGGCCAAAGTCGGCATGTGCGTCAACAAA
TGAAGAGAAGGCAAAAAATGCTAAGTTAAAACAGAAGCGAAAGATCAAAACAGAACC
AAAGCAGATGCATGAAGATTACTGTTTTCAATGTGGAGATGGTGGAGAGCTGGTCATGTG
TGACAAAAAAGACTGTCCCAAAGCATACCACCTCCTATGCCTTAACCTGACTCAGCCACC
ATATGGAAAGTGGGAGTGTCCGTGGCATCAGTGCGATGAGAAAGGGGGGCCCTGGTTTC
CTTCTGTGAATTCTGTCCACATTCATTTTGTAAAGATCATGAAAAGGGGGCCCTGGTTCC
CTCTGCACTGGAAGGCCCGCCTCTGCTGCTCGGAACATGACCCCATGGCTCCTGTGCAC

Sequence 89

Sequence 90

Sequence 92

TABLE 1 18/467

TGAAGGCTGCAGTACCGTTGGTTCGTGCTGGACTACAATGCAGGACTGCTCTCCTACT ACACGTCCAAGGACAAAATGATGAGAGGCTCTCGCAGAGGATGTGTTAGACTCAGAGGAG CTGTGATTGGTATAGACGATGAGGACGACACCCTTCACAATAACTGTTGATCAGAAAA CCTTCCATTTCCAGGCCCGTGATGCTGNTGAGCGAGAGAAGNGGA Sequence 94

ACGCGTCCGCGGACGCGTGGGTGCGGCCCGGCCNCCCTGGACGAAAGAAGAGGGCCCCTC CAGGCCAGTCTGGGCACCCTGGATAGCGGCTGCAGCCAGGCATGGCCGACTCTGCACAG GCCCAGAAGCTGGTGACCTGGTCACAGGGGGGCTGTGGCTTCCTGGGAGAGCACGTGGTG CGAATGCTGCAGCGGGAGCCCCGGCTCGGGGAGCTGCGGGTCTTTGACCAACACCTG GGTCCCTGGCTGGAGGAGCTGAAGACAGGGCCTGTGAGGGTGACTGCCATCCAGGGGGAC GTGACCCAGGCCCATGAGGTGGCAGCAGCTGTGGCCGGAGCC Sequence 95

CCCCGCGTCCGAGGTGACCTCCTTGGCCCAGATCATCTTAGAGCCAAGAAGCAGGACCAT
TCGTGGTTTTGAGGCCCTGATTGAAAGAGGAGTGGCTGCAGGCTGGTCACCCATTCCAGCA
GCGCTGTGCACAGTCAGCCTACTGTAACACCCAAGCAGAAGTGGGAGGCTCCTGTATTTCT
TCTCTTCTTGGACTGCGTGTGGCAGATCCTTCGTCAGTTTCCCTGTTCTTTTTGAGTTTAA
TGAGAATTTCCTCATCATGCTCTTTTGAGCATGCTTATGCCTCACAGTTTGGAACATTTCT
GGGCAACAATGAAAGTGAAAGATGTAAGTTGAAGCTACAGCAGAAGACGATGTCTTTGTG
GTCCTGGGTTAATCAGCCCAGTGAGCTGAGTAAATTCACCAATCCCCTCTTTGAAGCCAA
CAACCTTGTCATCTGGCCTTCAGTTGCTCCGCAGAGTCTTCCACTGTGGGAAGGTATTTT
CCTACGTTGGAATAGATCCTCTAAGTATTTGGATGAAGCATATGAAGAAATGGTTAACAT
CATTGAATATAAAAGAATT

Sequence 96

CGCCNCGCGTCCGGCAAAGCAAAAGGGAAATTATTTGGTGGATGGTAGCTCAAAATTGGA
ACTCTTGTTCTAATTCAGTTACATTGGCTTTACCCTCCTTAGATTTTTCATCAAAGGGCT
GTCCCATTGCAATCTTACTAAAACATTTTGTTAAAATAAACTCTTTTCCTTTTTATATTA
ATAATTAGGCTTTTAAAATAAAGATGTTATTCCTTTAAAATGGTGGGCTTACCATCATTGA
AGATGTCACCTCAGGTGGCCTTGCTTGATCAAAACGCCTTTTTTAAAAACCAAGCTTTAAA
AACATGTTTATAATTTCATGAAGTACATATATTGTTCCCATAGTCTTCAGCTTTAAAA
CTATAAATATGCCCAAATTTTGTTATTTGCCCTACTTTAAGTAGGTTTATTGNGTTTGTT
TTTTTCAAGTACTTGTTTTTCTCTGATAAGACTCAGGAATTCTGAAATGTGAAAATGNCT
CAATT

Sequence 99

TABLE 1 19/467

CNCGCGTCCGAAATCGTTGCTACCAANTATTCAAAACCCTTTGAGTTTACATACTAGTTACCTTAAAAATTANTNCCTGACNCTCNTGANTTTGGGNGGAAAGCCCTTGTNTCNNCTCTCTAATGNACTCTCATGGGTTTTTTTGTATGATTTGAATATNAATGTGCCTAAAGAATTTTTGCTCTTAATCTATGNATACATACTTGAACAAATCATTCTTGCTTAACTGCTGATCTTTTTGTAAAAACTATTG

Sequence 100

GCCCGCGTCCGGAAGCAACAGTTTGGCAGCCTGGGGTACACTCAGGTTATTCGTT
ACAACTATTATTTGATGTCTTTTTTTAAACTCAGGTCATCCACTTTTGACTGTCATC
CATGGAAGAGCTCTTATTAAAAGCCTCAGACTTTCGGGACCTATGATTCTTTGGCACAAC
CTTTTGGAAAATTCTTAAGCAGGGATGAAGCAAACTTGATTGGAGTTGGGGAAAAAGAAG
ACAGATTAGTATTTTTCATGCTGACAAAAAAATAGCTGCTATGACTTTTCCCGCAACGTGG
ACAGGGGCCAAGTGAAGCTGAACTGGTCATGGTCTGTCGCCCAGTGTTCCCTTGTCGTCG
GCGATTTTGCCCCCGACCCTTCTTGGTGGGCTTAGTGGTGGCAATCTGTCTCTTCTACCA
GACTCTGACCCTCCGAGGGTCGAGGAAGCTCACAGCCGCTGCCCCTGGGGCTGTCCCACA
CACATCCACTGAAA

Sequence 101

Sequence 102

Sequence 103

Sequence 104

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GCAATCCTGGCGGCGAGCAAGTATGAAAGAAACGAACCGGCGGAAGTCGCTGCATCCAT

Sequence 105

CGTCCGCGCAGCGCTTGAATCCCGTGGCCTAACCGTCCCTCGGAAGACCGGTCCCGCTCGGGAGGCTCTGCAGTCGCGCTCGGGGTCAGGGCCGGGGGCGAATGTGGCTCGCGTTCTAGGCCTCCCTGGGTTGGAAAAAGACTATGTTAGCAANGTGTCACGCCATGCTTTTGCCAACTTTCCAATTAAAGGTTGACATTCCTGCATAAGCATTTCTCTGTGAAAATGTCCTTGCCTCTTACAGAGGAGCAGAGCAGAAAAAGATTGAAGAGAATCGACAAAAGGCTCTGGCCCGCAGAGCTGAGAAGTTATTGGCAGAACAGCATCAGAGGACTAGCTCGGGCACCTCCATTGCTGGCAACCCCATTCCAGGCCAAGCCAACTTCCCAAGGGGAGTCTTGTAAGGCCAAGTGAGCCATTGGTGGTGACCAAGACCTCATTGGTGGTCATTTTCAAGCAACAGAATCTCAGTAGCTCATCTAATGCTGACCAAAGACCTCATGATTCCACAGTTTTCANGCAANGGGAATATGGAAA

Sequence 107

GCGTCCGTCTNAACCCTAAAGCTAAAAAGTCATTGTGAACCTTTNGGTCTGATGCTAAAG
AAGGGAAAACAGGTACAGGAAATCCCATGTGGATGCTTACTTTNCAGGATTTCCTGCCATG
ATTCCAGAATCCCACAGCTNCAACATGATTGCAAAAAAGACTCCCTGCTCATTTTNCCTCA
GCATGCACAGCGCTGTCCTGTCTCAGTTGCAACTCGACAGAGCCGCATTTACTCCAGAAC
CCAATCCACACCTGCTCATCCTGCCCCGAGAGGAGTGCCTGAAGCCAATAGCAGGGAA
CTAGAGCAGACTTGGGTGGATCTTCATTGGATATTAGGTATCTTGCCCTAGATAGGCAAG
CAGTGGCCTTACAGATGCTGACAGATGATCTGATTAGATGCACAGNTGCTGGGTGGCGTC
TGGGGCCAGTCTATTGGNCAGTTCTGGGAGNGGGAACTATTTGGGCTCTGCAAAGATG
Sequence 108

AGAATTGTGTATGCCTTGCCTATCACGGTACAGCACGAAGCCAGGCTCCTTTCTCCACCA
AAGAAGATGGAACCAGACTGGAATTCTGTCTCCAGAGAGAAACCCAGCTGTTTGGGTCAA
AGACAGATGCTTCAGACTTGGGTGGGAAGGTGAAAGATGGCTATTTAGAAAGCTGGTGGC
ACGTTTTACATAAGGGAATGTCAGATGGGAGATGCTAGTTGCCATTTTAACAAAGCAGGT
AAATCGGTAAATTTTAAACTCTGTCCATGTTCTGTTAGAACTCAGGGACAAGGGATCCAT
GAAAAAG

Sequence 110

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Sequence 111

CGCGTCCGGGCGCCGGTACGCCTGGTCCCCGCGTGGAGTCTTTACTCAAAACAGCTCCCG CCTCAGGCCGAGATGAGGAGCCCTTCANAATAGCTGCTGTCTCTGGGNGGACCCGGGCGT CCTTGGCAGCCCAGCTGNTCTGGACAAAGCCCTGCCAGTCAGGCCTCCGCTGGCAGGAAC CATGGCAGAGGCTGGGGATGCTGCGCTATCGGTGGCCGAGTGGCTGCGGGCATTGCACCT GGAGCAGTACACGGGGCTCTTTGAGCAGCATGGCCTGGTGTGGGCCACTGAGTGCCAAGG CCTCAGCGACACCCGCCTGATGGACATGGCCATGCTACTCCCT

TGTCGACCCGCGTCCGCGGGANGTTCATGGAAACGCAGGACACGACAGAATTGTGTNTG
CCTTGCCTATCACGGTACAGCACGAAGCCAGGCTCCTTTCTCCACCAAAGAAGATGGAAC
CAGACTGGAATTCTGNCTCCAGAGAGAAACCCAGCTGTTTGGGTCAAAGACAGATGCTTC
AGACTTGGGTGGGAAGGTGAAAGATGGNTATTTAGAAAGCTGGTGGCACGTTTTACATAN
GGGAATGTCAGATGGGAGATGCTNGTTGCCATTTTAACAAAGCAGGTNAATC
TTAAACTCTGTCCATGTTCTGTTAGAACTCATGGACAAGGATCCATGAAAAAAGACCTGTG
ATGTTTCNTCTGGCGCTTTACTGGCCTGGGCACACCTACCAATCTTTTAGGATTTGACTG
GTTCCATTACATTTCCT

Sequence 114

Sequence 115

AGTTCAGTCTGCAGCAGTCCCTGCACCCACTTCCCAGTTGCTTTCATCTNTGGAAAAAGA TGAGCCCCGTAAAAGTTTTGGCATCAAGGTCCAGAATCTTCCAGTACGCTCTACAGATAC AAGCCTTAAAGATGGCCTTTTCCATGAATTTAAGAAATTTGGAAAAGTAACTTCAGTGCA GATACATGGAACTTCAGAAGAGAGGATTGGTCTGGTATTCTTTCGGCAGCAAGAGAGCCA AGAAAAAGCCTTGACTGCATCAAAAGGAAAACTTTTCTTTGGCATGCAGATTGAAGTAAC AGCATGGATAGGTCCAGAAACAGGAAAGTGAAATTTCGCCCCTTTGGATGAAAAGGA TAGATGAATTTCACCCCAAAGCAACAAGAACTCTNTTTATTGGCAACCTTGAAAAAAACC Sequence 116

CCCGCGTCCGCACCAGGCCCGAGTCTTCCCTTCATGGAGGGTGACGTGAGCAGCAAGGAT
AAGATGGGCAAAGGATGGATGGGACATATAAAAAAAGCTCTTCAGGAAGCTGCAGCAAGG
TTTGAGGAATTAAAGGCCCAAAAAGAGCTAAGACAGCTGCAGGAAGACCGAAAGAATGAC
AAGAAGCCACCACCTTATAAACATATAAAGGGTCTCCCTCTGTGACCCAGGCTAGAGTGC
ATTGCTGCAATTTTGGCTCACTGCAACCTCCGCTTCGTGGGCGCAAGTGATTCTCCTGCC
TCCTGCCTCAGTCTCCTAAGTAGCTGGGATTACAGACATGAGCCACCAACGCCTGGCTAA
TTTTGTGATTGGCAAAAAAAGAGATTTTGTGACACATAAAGATGATATGAAATTCAACTTT
CAATCAAGTATCCAGAAAAATTTTA

Sequence 117

CCACGCGTCCGGCCCTTGCCCCTGTCNCACANGAATGGACCCACGGCCCCACCCAGCGCC

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Sequence 118

Sequence 119

CACGCGTCCGGTTTTACTGCTCTTTTGCCATGTGGTAAAAAGAGGCTGAGACATATTTAAG
AATTCCAAGAGGATATTACTGTCCAGAATTTCAGACACTGATGAGAAGTTTTTAATTGTT
CTTTTTTATTTGATTTTGGAATTCAGGTGCACTCTATTCAAGTGCAAGGATATCAGAAGT
TTTTTTTTATTTAAAAAAATTTTTTTTTCGAGATGGAGTTTCACTCTGTTGCCCAGGCTGG
AGTGCAATGGCAGCTTACTGCAACCTCCACCTCCTGGTTCAAGCGATTCTCCTGCCTCAG
CCTCCCCAAGTAGCTGGGGATTACAGGCACCGCGCCAACACACCTGGGCTTATTCTAATT
TAAGTAAGAAAATGGGAAGTCTTACCCATNTTTGGTCAAGGCTTGGGTCTTCGAACCTNC
TGACCTTAANGGTGATNCCACCCCANCTTTGGCCTCCCAAGCCGTGCTNGGGATTATAGG
GCATGAAGCCCACCCANGCCCGGNCCCAGGATTTTTATATTTAAGCCCTTCTTGCTCTTN
AAAAAAAAAAAAAAAAGGT

Sequence 120

Sequence 121

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TGGAGCGGGGGGGGCTGAAAGCCATTTCCTTTCCCGTGAAGAATTTTTATCAGTGCAAGTAACAAAATATT

Sequence 123

CGCGTCCGCTNAAAAAAATAATACCAAAAAAAAGTTTTTGTAAAGACAACGCTCTCGCTGT GTTGCCCCGCCACTGTGGCCTCCTTAGCTTCTCCCTGGGGCCTGCTGGACCTTTCCATA CTCCAGAAACTAAAGGGGGTCCAGGACCCTGCTTNAACCCTAGGATCCCGCATCTTTTT TTTTTTTTTTTGGACGCAGGGTCTTGCTGTGTCCCTCAGGCTGGAGTGCAGTGATTCACT GCAGCCTCAAACTCGTGGGCTNAAGTGATTTCTTTAGCCTCAGCCTTNTAAGTAGCTGGG GACTACAGTCATACACCAACATGCCCAGCTAANTTTCCTTTTTTTAATTCTTGTAGAGNA TGTTTGAGACGGCTTGGGCTNTGTTGCC

Sequence 124

CCNCGCGTCCGTGCTGATAAAACTCCTTTGACCTGACGATTGCTCTAAGTCCTAATTGCC
ATATTTATATTCCCATAGTAAGAGTGTTTGGAGATAGTGTTTGAGCTTTTTTGCTGGTGT
TAAAAATGCATAATGAAAGATGGCACNAGAGAGGCATATTATATCCAATTCATGAAGTTG
TTTGTGTTAACAGAAAGCTTATTTTAATCACTTAACATTGTTGATTTGTCTAATCACAGT
AGCGCTATTGATTAGGAGCCTGACCTTTANATGGTTGACTTGTGAGTGTATTCAATATGG
TGAAATAANGGTGTTTGATATATGGCTGCAGATTTTAGAAGGTGTCATTAGCAAAGGTAT
ACGGAATAAAATANGGGTTATAGTATTCCTTACTCAAATTCTGTATGTGCTAGAGCTGGC
TGGAGTCTGTTGGCATGCTCATTTGGTGTAAGGNCCGNTAAGGACTATGCT

Sequence 125

GCCCGCGTCCGCACTTTGTATTGATAACTTAAAATGGCATCAGTTTATCTTAGACATCA GCTTGCTTTTTATCTCCTTTTTTAGTGAGTGAAATAGAGCAACTAGCATGCCTGTGTTCC CAGCTACTTGGGAGGCTAAGGTGGGAAGATCAATTGAACCTAGGAGGTTGAGGCTATAGT GAGCTGTGATTGCACGACTGCACTCCAGCCTGGGCAATGGAGTGAGACTCCTGTCTCTAA AACAGCAACAACAAAAATAAAGCAACCATAGTGCATAAGGGAAATTAAATGTTCCCTATA GAAATATGTGTATGTCTGTGATAAGTGGTATGCAAATGCTAATTATTTTATAAAATAAAA GTTCAGAACTATTCTTATCATTGCCACTTGAACAATTAAAGGGTTTGCTTTATTTCCTAA TGTTTAATAGGAACCCTTTGCTTCAAACAGCCTTTGTTGAAAATCATGTAAAAAATTTGTTA

Sequence 126

Sequence 127

CNCGCGTCCGCGGTCGCGGGGCGGACGCGNGGGTTCGTCCTGGACAAGTCTGGGAGTGT GGCAAATAACTGGATTGAAATTTATAATTTCGGNNAGCANCNGGGCGGAGAGATTCNGTG AGCCCTGAAATGAGATTATCTTTCATTGTGTTTTCTTCTCAAGCAACTATTATTTTGCCA TTAACTGGAGACAGAGGCAAAATCAGTCAAGGCTTGGAGGATTAAAACGTGTTANTCCA GTAGGAGAGACATATATCCATGAAGGACTAAAGCTAGCGAATGAACAAATTCAGAAAGCA GGAGGCTTGAAAACCTCCAGTATCATAATTGCTCTGNCAGATTGGCAAGTTTGGACGGTC

Sequence 128

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Sequence 129

Sequence 130

GCGTCCGGTGGCATCATGACTTCTGGGGCAGTAGACTGAGCAGCAACACCAGCCACAAGT
CCTACCGGCCTCTCACCGTCCTGACTTTCAGGATTAACTACTACCTCTCGGGAGGCTTCC
ACCCCGTGGGCTTTCACGTGGTCAACATCCTCCTGCACAGTGGCATCTCTGTCCTCATGG
TGGACGTCTTCTCGGTTCTGTTTGGCGGCCTGCAGTACACCAGTAAAGGCCGGAGGCTGC
ACCTCGCCCCCAGGGCGTCCCTGCTGGCCGCGCTGCTGTTTGCTGTCCATCCTGTGCACA
CCGAGTGTGTTGCTGGTGTTGTCGGCCGTGCAGACCTNCTGTGTCCCTGTTCTTCTTGT
TATCTTTCCTTGGCTACTGNAAAGCATTTAGAGAAAGTAACAAGGAGGAGCGCATTCTT
CCACCTTCTTGGGTGCTGCTGAGTATCTTTCTGGGAGCAGTGGNCATGCTTGTGCAAAAG
AGCAAGGGATCACTTGTGCTGGGTTTAAAATGCCGGAATTTGACAATCTTTGGGTGATAG
GC

Sequence 131

Sequence 132

CGCCNCGCGTCCGAACAGGCCGGGCACCAAGGCGCAGGATTTCTATAATTGGCCTGATGA
ATCCTTTGATGAAATGGACAGTACACTAGCTGTTCAACAGTATATTCAACAGAACATAAG
AGCAGATTGCTCCAATATTGACAAAATTCTTGAACCACCTGAAGGCCAAGATGAAGGTGT
GTGGAAGTATGAACATTTAAGGCAGTTCTGCCTTGAGCTAAATGGACTTGCTGTCAAACT
TCAGAGTGAATGCCATCCAGATACTTGCACTCAAATGACAGCAACTGAACAATGGATTTT
TCTTTGTGCAGCTCATAAAACTCCAAAAGAGTGTCCTGCTATAGACTATACTAGACACAC
ACTTGATGGTGCTGCATGTCTTCTGAATAGCAATAAATATTTTCCCAGCAGGGTTAGCAT
AAAGGAATCATCTGTAGCGAACTAGGATCAGTATGCCGTAGGATTTACAGAATATTTTTC
ACATGCTTATTTTCATCATCGGCAGATATTTGGATGAATATTGAAAATGAAAC
Sequence 134

TABLE 1 25/467

GCGTCCGCGAAAGCTGGGAAGCCAGGTCTACCTGCCCCAGACGAATTGGTGTACCAGGTG CCACAGAGCACACAAGAAGTATCAGGAGCAGGAAGGGATGGGGAATGTGATGTTTTTAAA GAAATCCTTTGAAGATGATGCTGCTTTTTACAAAGCATCGTTTTAAAGCACATGGCCTTT TTTTTTTAATTATTAGTGGTAGTAATATATAGAATGTATTACATAACTGTCACTGAAGT GGTTGGGGAAAATGTGGTGACTGAGGTACAGGAAACTACTAATCTTGCCATCTTGCTTTA AGGTGTTATGGTGGCACAGTTACTGCTCGCCTGTTAAATTTCAAATGTCCTGTTTGATAC TACTGGAGAACACTATTTTTAATACAGAAAAAGCTCCCTATAATGCACTTCAGAGAAATT

Sequence 135

TCGACCCACGCGTCCGGGAGTCCCCCCTGCCCCCATCAAATGCTTCCTGCAATACTTTG
CACACCAGAGACTGGGCCTCCCCAGATCCAGGGGACCCCTGGGGGAGTCCCCA
GGGCCAGCCCCTCCAGGCCAGCTGCACACACTTGACACTGATTTGCACAGTCTTGCACAA
ATAGGGGGTAAGAGCCCAGTGGCTGGGGTGGGCAATGGGGGTAGCCTCTGGCCTAGGGAG
TCCCTGGCACTGCCAATGGGCACAGTCCCGAGCACACCCCCTGGCCCTGGACCCCA
GGCCCCTGCCCCACCAAGCGAAGGCTGCTTCCTGCTGGAGAAGCCCCAGATGTCAGCTCT
GAGGAAGAGGGGCCAGCCCTCCGGAGGCCCGGGGATCCCTGGGCCCCAAAGAG
CCTGTTTTGGACCCAACAGCCACCCTTCTGGAGCCACCTGCTGCCCAAAGAG
CCTGTTTTGGACCCAACAGACTGCGGTCCCATGGGGCGAAGGCCTGAAAGGAGCCCCCCC
CTGAAAGCTTGAGCCCCCTTCGAAAGCCTNCGGAAGGGCCCAGGCCTGCTGAGCCCCCCC
AGT

Sequence 136

Sequence 137

TCCGATTTTTAAATCTATTGGCCGTGTTGTCCTACCTGAAGTTCTTCAACTGCCAAAAGC
ACAGCCCTTTTTCTCTGAGCTGGTGGTTCTCGCTAACACTGACAGGGGTCGCTTGTTCCT
GTGCAGTGGGCATCAAGTACATGGGTGTTTCACGTACGTGCTCGTGCTGGGTGTTGCAG
CTGTCCATGCCTGGCACCTGCTTGGAGACCAGACTTTGTCCAATGTAGGTGCTGATGTCC
AGTGCTGCATGAGGCCGGCCTGTATGGGGCAGATGCGGATGTCACAGGGGGTCTGTGTT
TCTGTCACTTGCTCGCCCGAGCAGTGGCTTTGCTGGTCATCCCGGTCGTCCTGTACTTAC
TGTTCTTCTACGTCCACTTGATTCTAGTCTTCCGCTCTGGGCCCCACGACCAA
Sequence 138

Sequence 139

Sequence 140

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Sequence 141

Sequence 142

Sequence 143

Sequence 144

Sequence 145

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GGCAGAGGCGGCGGCGGGGGAGGACAGCACGGCCGAGGCTGCCCAGAGGCGCCTCCTC CACACCCCCCGCCGCAGCACCACCGGCGACAGATTTTTTAAAAAATGGATTTGGCCAACC ATGGACTTATTCTACTGCAACAGTTAAACGCTCAGCGAGAGTTTGGTTTCCTGTGTGACT GCACGGTTGCAATCGGCGATGTATACTTCAAGGCACACAAATCAGTTCTTGCTTCATTCT CCAATTACTTTAA

Sequence 146

NACCACGCGTCCGCCNCGCGTCCGCTTGCACCCGGTGAAGAGCGTGCGTGTGCTGAGGCC GGAGCCGCAGACGGCTGTGGGGCCCTCGCACCCCGCCTGGGTGCCCGGCCCCGGC CCCCGCCCNCGNCCNCGCCCCGNCCNNGCTGCGGAGGGCTTGGACGCCAAGGAGGANCA TGCCCTGGCGCTGGNCGGCACAGGCGCCTTCCCGNTGGACGTGGAGTAC Sequence 148

Sequence 149

Sequence 150

CACGCGTCCGGCCTGCTGTTNACCTGCGGGACCCCAGGAACCTGGACTTGTTTCTCAAAG
TGGTTCATGGAGATGTCACCCCCTACGACCTGGTGCGGATGAGCTCGATGCAGCTGGCCC
CCCAGGAGCTGGCCGCTGCGGGACCAGGAGGAGAAAAGGGGCCTGAATATCATTGAGC
AGCAACAGAAGGAGCCGTGCAGACTTCCAGCCTNCAAAATGACCCACAAAGGGCGAAGTGG
AGATTCAGCGGGACATGGACCAGACACTGACCCTGGAGGATCTGCTGGGACCGCAGATGT
TCATGGACTGCAGCCCACAGGCCCTGCCCATCGCATCAGAGGACACCACGGGGCAAGCAT
GACCACCACTTCTTAGACCCCAACTGCCACATCTGCAAGGACTGG

Sequence 151

TABLE 1 28/467

TGGGTGCCACAGTAGGAATGAAATGATGGGGACTTTTGGAAGCCCCTGGACTTGTGGCCCCTGTAGAAGAGCAGCTTGGGCAGGGTGTGATGGCCATCTCTGTCTCTAGGGGCCCTGTGG

Sequence 152

GTTCGACCCACGGGCGTCCGCGGGACCGCCGTGGGNNNNACATACTATGCGNACAGGCGC
GTTGNACACAAANGGCCCATTCCTGTAGCCTCACACTTGACTACACATGGGGGANTCACT
CGGATTCGGNTCTCCACGTGGNNGNTCTTTGTTCTGTACTCTACGTAGCTTTGGCTTTTG
TTTTCTCGTCGCAACAGGGCATGAGACTTCGTCGACCTTNGGGGTCTGTATAGTCTTTGA
CTTACTACGTGTAGGTCTCAATACAAAGTGGGANATANTCATATCCGTCCGCGAAAAGTA
ATTCTTGGAAAAATTTACCCTTGTCTCCCGCNTTATGAAACGTGAACTAAGTAACTCACT
TTGCCCCTGGGGCGCCTCTNTTTAACANTGTTCTTTTGNCGAAATCATCATAACCTTCAA
CTGAAAACAATGTGGTCAACAAACTGACTATGGAGGTCTTAGGCTCNGTCTCTAAGATCT
TTAACCTTGTTTATCGGCGCGTGCGGCGTNGTCCGAACGAAGAGACTATAACCCGCACTA
TAACNAAAACTCTTTTTTTAATCCCACCACCTCGTGAGGGANGGGCCCTAAGACTGAAACT
GTAGTAAGTCCTATTGATTTGCGTAGGAGGANTTAGGAAA

Sequence 154

Sequence 155

Sequence 156

Sequence 157

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Sequence 158

CGACCACGCGTCCGGGGACTCAGGCATGCACCACCACGCCCAGCTAATTTTTGTATTTTT
AGTAGAGACAGGGTTTCTCCATGTTGGCCAGGCTGGTCTCGAACTCCTGACATTCGGTGA
TCCACCCGCCTCGGCCTTCCAAAGTGCTGGGATTACAGGTGTGAGCCACCTGTGCCCAGCC
CCTTCCTGTTGAGTAAAAGGAAGAACTTCAGGGTAAGACACTGTACAGTGCCCAGCATCT
GGAGAGCCGCCAGCATTACCCCTGCCTTAGGAGGTAGTCGTCTCCTCATCACTACAAGGT
ATTGAAGCCTGAGGGCCCCTGGGCAGGACGATAGAGTGAGATTGCCCTGGGGACTCAGGA
AAGGAAACATGCCGTATTTNTAGGGAAGGAGCTGCTGCTGCCTCTCAGTGACTCTGGTTC
CAGGAGGGAAGAGCCGAGAGCTAGGGTTCCCTTTCATAGGGAGAAACCCAGCAGGGTTTG
GGGTGTTCT

Sequence 159

Sequence 160

Sequence 161

Sequence 162

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TTCCCAGCAGACCTCTGAGGTAGGGTACTAGTATGATCCCCATTTCGTACATGAGGAAAC TGACACTAAGGGACATAAAATAAGTTTTTGAAGTCACAAAGTGAATAAAAGGAAGACCAG GGTTTTAATTGGAAGCCCATA

Sequence 163

TAGACTTTTGCAGTGTTAAACACAGCTTCCTTAACTCTTAGAACTGGAAGTTGTAGAGCT CTCCTTTTGGTGCCTTTCCAGCCTTTATACACACACTATTGTAGCTTTCTTAGGTTTGATAG GTAGCGTTTCAAGTAGTTTAGCTGAGACAGNGAATGTATTAGGTTCAACATGACCTTGTG TTTATTTGTGTTTGCCAACAGGATGCCTTATTTGTTTGAGAAAAAGATGTACTAGTGTC ATTCTAAACTATCTCCTTTTTTAGGATTCTAAAGAAGTTAATCATCCTCTTTTGTTTAT TTTACCACCATTTAGTGCCTTAAATCCTATCAAGAAAGCAGTGTTACTGCTCAATGCCCA AATAAGACACGCGGATATTGCTATTGCTTTTTGAGTTAACAGGCCNACTTTTTATAC TTAAAACCTCA

Sequence 164

Sequence 166

Sequence 165

Sequence 168

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Sequence 170

Sequence 171

TTTAGGGAGCCGACCCACGCGTCCGCTTGGCAAACCTCCGGGGACTGTCAGAGGAGGAGAGAGGAGCGAGAGAAGCCGAGAGAGCCCACCTCCCCCCCATTGAAGAGCAGTCCCAGCTCATCTCCATCC TGAAGCGGAGGTCAGATGAGGCCCTGGAGCGCTGCCAGATCCTAGAGCTGCAATGCAG AGCTGGAGAAGATGATGCAGGAGGCTGAGAAGCTCAAGGCCCAGGGTGAGTACAGTC GGAAACTAGAGGAACGCTTTATGACCCTAGCAGCCAACCACGAGTTGATGCTCCGCTTCA AGGATGAATACAAGAGTGAGAACATCAAGCTGAGGGAGGAGAATGAGAAGCTGAGGCTGG AGAATAGCAGCCTCT

Sequence 172

Sequence 173

CGTCCGGTGACCCATTAAGTATATTTCGTGACCCANAGTTTGAAAGAGATTATAGGTGTA GCTTTGCTAGTTTGTAATTGATATAGAACAGTGACTATCAGGGAAGNTGAAGAACGGCNA ATTGAATGTAAATCATGTCTGGATGGTGAAGATTCTAAGAATGCANCTAGGGAAAGGGCT GCAAAAAGAAGGTGGCAGACTAATGTAGAATGGTGCAACCAGATGAAGACATGGGTGGCT TTAGGAATTCCAAAGTGGCCGTGAAGGCCAGGCACGGTGGCCCACGCCTGTAATNCTAGC ACTTTGGGAGGCCAAGGTGGGTGGATTGCTGAGCTCGGGAGTTCGAGACCAGCCTGACCA ACCAGGTGAAACACCATCCCTACAAAACAT

Sequence 175

GGCGGCGGCGGCGGCGGGCCGGGACCCAGCGGGCCAGGTGGGGACGCGCGTNGCGGG TGCGGAGATGCCGTGCGGGACTGGGGCCACNTTGAGCCGCCCGNCTCGTCCCCGCCTTC

TABLE 1 32/467

TGTGGGAAGGATGTCCCCGGGGGCCCGGATGGCCGCCCAACAGCGGCCCCTCGGGGGCCCTA CGGCCCCTGGCTCTCCTGGTGGCCCTCGCCCTGGACGTCGTGAGAGTGGACTGTGG CCAGGCTCCCCTGGACCCTGTC

Sequence 176

Sequence 177

CCTTGTNAGGGGACACAAAGAAAAATTGAATAAACTGTATGATTTAAAAGATTATCGGGA GAGTTACCTCCCGATATAAAAGGAAGGATTTACAGAATGTGACCTAAGGTCTGGCGTAAA TGTGCACCGGAACCGAGAAGGCCCGGATTGTCATGGACGATGAGATACACCGGAATATCA TGGACATATTCTTTAAAGCGCCCTTTATCTTCAAATGCGGCACGGAAACCGGAGGCTTTG AAGAACTCAAGGAAGCGCGGCACGATACCGCCCGCAATAAACACGCCGCCAAATGTCCCG AGATTGAGCGCCAGATTGCCGCCAAAACGGCCCATAATGACGCAAAACAGCGACAATGCG CGGCGGCAATCGGTGCAAGCTGTCAGCCAGCGCCGCGTTCGGTAATATCTT Sequence 178

Sequence 179

Sequence 180

CCNCCGCGTCCGAAAAGACAAGACAGCATACTGTATTTTTCCTCTTAAAATTCAATGTTA
CAATTAAATGATTGTTNTCTGAGAATAAGTTAGCTTCAGCTTTCTAATCGATGTTCCC
ACATCTACAAATTGATATGAAAAATTATTTTGAAATGCACACTGCAAAATGGTGAGAATA
TGAAAGTTACCTGGGAATTAAATCAGAACTGTCTCCATATGACTATTTCCAAGTCACAAT
CATAACTTTCTTAATAGCAATGGTTATATATGTGGCCAGATAGTATTCAGTTTCACAGTA
ATGTCTCGGTCACATAAAGATAGCANAGCATAGACATAGTACAACAATTTATTATTTCTG
CTGATTGCCAAATGTGCATAAAACTATAAAGATATATTTTCCAGCCCAGGTGACAGAGAC
CCTGTCTCCCNTTTNAAAANCTTCATGNTAAAGGTGCGGCCGCTAGACTAG
Sequence 181

CGCGTCCGCTAATCAACTTTTAAAAATAATGTTTTACGGCCGGGCGCGGTGGCTCACGCC

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Sequence 182

Sequence 183

Sequence 185

GTCGCCCGCGTCCGGGCATTTGTATTTTCAACAATTGTTCTCAAATTTAGAAAAGAGAC
ATCGCAAGATGGTGAAATAGGAAGCCCTGGGCCCTCCTTCCCTCCACAAACACACTGATT
TGACAACAGTTCATGGACAGATTCCCTTTATAAGAAACCAAGAAACTGTTAAGAGGCTCT
TATACCCCAGGTGAGTGCAAAATCATCCACATCAAAGATAGCTGGGAAGTTCAAGACACC
TTCTTTCCGTAATTTCTAAACTGGCACAGTACTATATGATTGAGATGAATCTCCCACAT
CCAAGCTTCCTGCTGGGGAGGAGAGGGGGAGGGTATACCATTATGTCCAATGTTCCAACTC
CTCTAGGAGCTACCCAGGTAGGAGGTGGGTCCAGCTCTGTCAGGCTTGTCTTAAGAGCAC
TGATTGAGGGTCTGGTATTCTCTAAGTGGCCCAGGACCATAAGAGCAGTGGATGGTGCTG

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GGGNTNNGNNGTGGGTTACCCATAACCCCCTGGTTTTTGG Sequence 186

Sequence 187

Sequence 188

Sequence 189

Sequence 190

CNACACATGCGGAATCATAGGCCTGCAAAGCTCCTGCTATTCACTATAACTCTGCCATGC
CTTAGGCACTTCCTAACCTAGAATTCTGAGTGAAGGACAACAATAACTATACTTTTGAT
TCAGGTATTACAAAGAAGTTAAGAGTTCATAAGGCACCTAAGTAAAGTCACATTGGTTAA
GAGTACATGTCTCCAGATACTCTTACATTTGCAAAGNAATTGCATTTCTGNATCTATGGT
CTGTAAATAAAATTGAAGAGTTGNGAGAATAAAAGCATGTTGTCTTTGATAAATTGTTTT
TACAAAACAGGCACAAGAGAGGCTTGAAGGGTCCTTGCTATCTTTTAACCTATTTTATAA
TCTTTGCTGCATAAGAAACAAATATGCTTATTTACATTCTATACTTAAACATATTATCAA

TABLE 1 35/467

ACTITIATTCTGAAGATAATACACATGAAGGCTTTAAACTTTAATCTTCAATATTTTT
TAATCTCCCTGATGAATTAGGGAAATAAATATTGGG

Sequence 191

Sequence 192

Sequence 194

Sequence 195

CGCTCCCTGGTTTCTTGTCTCATGAANAAGAAAAAATCCTAACTGTTCTTGATGATCTTT
AAGGCTCANAATGATCTGGACAGAGGTATTTACCTTGAAGCTCATAAAGCATAGGCCTTT
CTCACTTGCAGAGTATCTTTCTGAAGCTGGACTAAATTGGTTAAGGCCACTGTACTTTTC
CACTTTGTCTTCTTTCCTGTCACACACCCTATCCTTTCAGGCTGTGTTGGGATGACAAA
AGCAGTTCTGGAGTCCTAAGGAGAAGATGAGTGGGATATGTTTCTGTGACCTGCAGTCAT
TTTAAAGTTTAGCTGTTGCTAGCTGACTCCATGTAAGAATACCTTCCAGGAATTTGATGG
CTGTGCACTCTGGCAGTGCAACTGGCATGGT

Sequence 196

CNCGCGTCCGGCCCTGATTGATGAAGCACAGTCAGTAAATCATCTCTTCATTCCCCAGTT CTTAAGCCAACATCAGCAACACTGAGAGAACATTAGATTAAAGGCAGGTATAGAAGAGAG ACTTAGGGTAACAAGTTAGTGGGTGCCTGAAGGCATGTGGGAAGAGATGTGGTAAAGGTG

TABLE 1 36/467

CTAAGCTGTTATTTTCCCTAAAAATGCTTCCCTTGCATTTATACTTATTAAGAATAGATA ATAGCTAACATCTATCCACTGCCTTTGATTCATGAGGCCCTCACGAATTGCCTCATTAGG TCTCCGACAGTATGGTACAACTACTCTTTATATTTTACAGATGAAGAAACTGAGGCTGGA CTGNTACCTTTTTGCTACACATCCTAATG

Sequence 199

AACCTGTTTTGTTAGATGTGAATCTAGGAAATACAATATATTTTTAATGTAAAAGNACTC
TTGCTTTACTTGTAAACTGATTTTCGTTTTTTTCCCCTCAGGCCATCAAGCCCTGTCGTC
CTATGACCAACAATGCTGGCAGACTTTTCCACTACCGGATCACAGTCTCCCCGCCTACGA
ACTTTTTAACTGACAGGCCAACTGTTATAGAATACGATGATCACGAAGTATATCTTTGAA
GGATTTTCTATGTTTGCACATGCCCCCCTGACCAATATTCCACTGTGTAAAGTAATTAGA
TTCAACATAGACTACACCGATTCATT

Sequence 200

Sequence 202

GCGTCCGGTTGAAGAGGGCAGGGAATAGGGGTGAGCGTGAACAGAGTCAGGCTGAT
TGCTGCAGGGTCCCTTGCATTAGTTCAGGTGAGAAGAGACCCGAGTAGGCCAGTGAGCCT
GGAGGAGAGGCTCTCTGTGTTTAATTGGTTTCCAGCTTTTTTTCTCTATTCATGTAGG
TTATACACGTTTCTTCTGTGAATTTTTATTTAAATGATTTTTTTGTTGTTACTGGATCTAC
AAACAGCCCAACTCCAAGGAATCTGGCATCTCTCAGTGAGCATACAGGTGACTTCATAA
TCTAACCGCATTAGTAACTGCCAAAATCGGAAGTAATTTCTCTCTGTTTAAAAGGCAGTG
AAACAAATTTTCAGAGCAGGTTTCTTCAACTGAACAAAATATTTTGGACCTTAAAGGTGG

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TATGGCTCTCCTGATCAGGGAGGGACAGTGAAAGGTTTGAGCTCTGACACTGNCCAGCTCTCTGGATACAACCAAGTGACTTTTTTTTG

Sequence 203

Sequence 204

CGCGTCCGCTGGGAGGCTGTGGGGTCTGCCACCCAGCAGATCTGTGTCACGGGAGTGGCG CTGTCACTCGTTGAGGTGGCCTGGTTCCTTTGGCCTTAGGGAAGGACAAACTTCAAC TCTGAGCCTTGATTGAGTGACCTTGGCCAAGTTACCTAGCTTTTCTGAGCCTCACTTTTT TGGCNATTAGATGAACCAGAGGTTTATTTCACTCAGAATCCTGTTCACGATGCTGGTATT TGGACCAGCCTGCGGGTTTATCCTGGGCTCTTTCTG

Sequence 205

Sequence 206

CCNCGCGTCCGGTTATGTACTTTTGGAGACTTCCATTAGAAATATTGGCAAGTCCCTGCT
TCGTGGCCATAGATTTAAAAGGCCTATCAATTTTAAATGTTTCGGTCATTGAGAGCTAAA
ACATGTAACATATCACAGTGTTATTCACCAGAAATAAAAAATCAAGAGTCTGCTCAGAGT
AGGTTAATATGAGTTCCTTTCTTCAGTCCAGCTGATGGTTTTTAGTAAGATGAACTGCCA
AGGAGACAATGAGCACTGACTTCTCGATGCATGACTTCATCTTGTTAGAAGGTGGGTTGC
CGGGCCGCGGTGGCTCACGCCCGTAATCCCAGCACTTTGGGAGGCCGAGGCGGCCGGATC
ACCGAGGTNGGGGGGATCGAGACCATTCTGGCTACACGGTGACACCCCGTCTCTACTAAA
TATACAAAAAATTGCCCGGCCGTGGTGG

Sequence 207

Sequence 208

CGTCCGGGAAAACAAGGGTTTCCGCCAACAGGCTGAGAGCAAAGGAGGACGCAGGAAAA CTATTTTAAAAATTGACCCAAGAGTTCAAAAGGCATATGGAAGCATTTAATGGGGGTGGG AGGTATCCTTGTAATAAGAATACCATGCATGTATTCCCACACTGCTCTTGGTGGTCTGCA AAGTGATTTCATATGTATTTTATGTCAACACCAGCACAATGAGGTAAGTAGGACTGTATA

TABLE 1 38/467

CCTCAGAGGCATTTGGTGATTTGTCAGAGTGGAGTGTAGTGTTGTTGGTGCCCAGATTTGA ATAGGATCATTTGAGTCTGATATCATCATGTTGCCCACCGCCTACTCAGCCTCTACACCC GATGAGGCCAATCTGCAGCTCACTACAGTCAATAGGAACAGGCAATTAACCCTTAAGTT ATATTTAGAAAGATTTCTGTCTAAAATAGATAAACTTGAAAGTATAGCTCTTCAAAATA ACGTATTCCTGTGTTGGCAAATATTTTCCAAACTCACAATCAACACATAGGTGTATTTCT TAGACTACTAGAAGTGGGGACTTACCCCAA

Sequence 210

Sequence 211

Sequence 212

CACGCCCGTGGCCTTGCTAGAGATCCATATAATGCAGTCATGCTGTTTCTTNCTCCATA
GTATGTGGGGCATGAGGAGGAGACAGGGAGAGGGTGGCTTCATTGNGCAAANGNGGAATG
GCTGTGCTTTGGGGCCAAGGAGATGCTGTCCTGCTGTAGCTGCTCTTGTAAAAGGTCAGGC
CTGCCCCTNTGAGGCTCCCTTTATCCTCCTAAATTCTGGGGCATCTACATGACGCTTTCT
AGTCCACCTTTGCCTNCGCAGATCATGGCTACTAACCTGACCTTTGTCTGTACTTGAGCA
CCCTTCGCGATTTAACTTNCATGTANCGTCCGACTTCTAATATGGATTTGAATTTNTTGA
CTGTTACTGCTCANAACAATCACCCTTTTTTGAGCAGNGAGCTGGNAGGATAATTGCCGA
CAAATGACATTNGGANCCGTTTTNAACCACAGGGGGCATGGGG

CGATCATTTATTAGAGTNATGTATTTAAGAACTGATAAATCATGGGCTTACCTACACAA TGTCTAGACACATGAGCAATGAACAAATAGCAAGGTCTGTGATATCTCATATGGCAATAC TAGGACTGAGATTATTTTTGTTACAATTAAATAATTGTCAGATAAAAATCCACAGAGATCA TTTAGAATGGGAAAAAAGTCTGATATATTTTGTTTCAGATTATAATCATTAATAGGGTAC CTGACAGTTTCAAAGTTGTTTAATGTTTTTTAGGTCTTTAACCTTCCTAATCCTACAAG GTGGTTACAATCCCACATATTATCCTTGTGTCAGGGGTCTCCAGCACCTGCCTTAGGGTC AGTGATTTGCTAGAAGTACTTACAGAACTCAG

Sequence 214

ATCTGACAGCCTGGAACNGCACCCCACACCCCCAGGTGAGAATCTGATGTTCTGGAGCATC ACACACACCCACAGGTGAGCATCTGGAGCACCCACACCCACAGGTGAGC ATCTGACACCCTGGAGCACCCCACACCCCACACCCACAGGTGAGCATCTGACCTCCCGGAGCAGCACCCATACCTCCAGGCGAGCATCTGAACCCATGGAGCAGCACCCCCCAGGCGAGCATNTGACCGAACAGAGCAGCACCCCCTCTA

Sequence 215

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Sequence 216

Sequence 217

Sequence 219

Sequence 220

TABLE 140/467

ACAGCCTGGTGGAGCTGGCGACCTGGTGGTGTCGCTGACCGAGTGCTCGGCCCACGCGG CCTATCTGGCCGCTGTGGCCACGCCGGGCGCCCAGCCCGCGCAAGN Sequence 221

GATTTTGGCTNCTGCAACCTCCGCCTTAGGGGTTCAATGCAATTCTCCTGCCTCAGCCTC
CAGATTGGGATTACAGGCATGTGCCACCGTGTCTGGCTAATTTTCTTGTAATTTTAGTAC
AAAAGGGGTTTCACCACATGGGCCAGACTGGTCTCAAACTCCTGGCCTAAAGCGGATCCA
CCTGCCTCGACCTCACAAGGTGCTGCGATTACAGGGATTACAGGCTGGGATTACAGGCAT
AAGTCACCACACCCAGCCTAAAAATTAAAAGTTTATACTGTATTGTTCACATTGTGATGC
AACTTTCCATATGTATTTCCAGAATCAACTATGTATCAAGGAATATTGAAAGCATAAAAT
GAGATCATGGTGAATTCTCCCCATTGTCATTCTTGNGGTAAGGGAATGAATGGTGG
Sequence 222

CGCNTCCGCCGAGCGCAGCAGTCTCCCCCTAACCTCAAAAGCCTCCTCAGAAGTAACCTG
GTATCAGTGGGCTGTGCAGATTCTTATAGTCTTCTTTGCCTTTATATATGAAAATAACTT
TGTTTTATGTTTGTTTTCACATAGGTGGAATTATACTGACTCTTACTCTGTGACTTGCTT
TCTTCACATGACAGTAACTCCTGGACTGTTTCTGTAGCAGCCACACAAGTCTCCTTTATA
TTGCCAATATCTATCTTTATCCCAAAGACAAGATGAATGTTCAAAAACGGTAATCCAAAC
TCACTTCTAAAAATGGGTGTGTTTTAAAGAAGAGGCTGCTCAGCTGAGGCAGTTTTGCTG
CCGAGGGGATTTGAGCAATGTCTGGGGACGTGTGTTCACAACTTGTGAGGGGGCTC
Sequence 224

CNTCCGCAATTACTGCCTTAGGCTAGATTCCCATGAATANGAATTGCTGAGTCAAAAGGT
TGACACATTNTTTAAAGGTTAGATACATATTAGTCAAAGTTTTTAAGCAANATGCTTTCT
AAGCCTNTTTGATCTTTATAANNCATTGNTCCTTTCTAAAAATATATAACTGTCTTCTGC
GTNCCAAGGATAATTNTTTTTATTAATATGGGGCTTCTTGTGTCTACTTCCTCCCCTTTC
GTTATTTCTTCAAAATGTTTAACAAACTAATACATTTCAGAACACATTATGCTTNCATCT
TGTCACTATTTGCAGTACCTTGTATCTCCTGGACTTTATGCAATGCGTGTGTGCACAG
ATGGAATATGTTNCACCATTTGGCT

Sequence 226

GCAGTGCCGGCGCAGTTGGGAATGGGAGTGCGCTTGCACAAGCGCCGACGAGCGATA GCGACGCTATGCCCTCTCTTGCCCAGGCGCCGGGTGGCGCGGATCAACCTGCTCTCGCAG CAGCCCCTGTGGTGGCCGCCGGTGATGATGCAGGAATCGTATTTCGACGGTGGNCAGCTT CGCTTTCGATCAACATCTTCGNCGAAGTTCCGCGTGAACCGTNCGGNATCGACATCGTGG

TABLE 1 41/467

CGCTGGCATCTGCCGCTATACCAATCATCGAAACCGCGCTGGAAGGTCGGGTCCAGCGCC CTGCAGAAGAGACGCCTCCAGCAGGACAAGGTGGCCTGCTCGACGAGCAGGCTACCCGAG TGTCGTTGAACAAGTATCGCCTTGGGTCT

Sequence 227

Sequence 228

CCNCGCGTCCGCAAGACAGGAGATTTCTTAAGGTCATATATGCACGATTTGCTTAAACGT CATATAGCATAACTGGAAGAATATAGAATCTACCCAAAGCCTATGCTCTTTCTACTGNAT TATTTGCTTATAATAGAGAATGCTAATCAGAATCACCTGAATAGTCTTGTAGAGGGTCAG TACACAAGCCTAGGTCCTATCCTTCAGAGAGGTGAAATGGAGGCAAATATATTCTGAAAG AGTTTCCCAGTTGATTCTGATGAGCACTCACAATTAAGAAGTGCTGCATTAAGAGCTGTA CATGGTGGCTTATGCCTGTAATCCCAGCTATTCCTGAGGCTGAGGCTGGAAGATCACTTG AGCCTGGAAGATCACTTGAGCCTGGGAGTTGGAGACCAGCCTCGGCAACGTAGTGAGACC ATGTCTTTTTTT

Sequence 229

NCTAGACTCCCCTCTGTATCATGGATCCCAACATCNAGGNATATGGNCATTTACGTGTT GGGATCTGCTCTGCCATTGNACACAGCTATATTCNATTGCCCCGGGNGTTGTGTATNTTT CCAAAAACGTTGAAAGGGAGGTTCAGAAGTATNCAGTTATTNGTATTATTAGTCGTTTTG AAACTGAGTNGAAAGACTCATTNANGAAAGNTCCATATGCCTTCTTGTCTGTCTATGGCT GGNNTGCTCNNGAGAAAAGTCCNCANTTATACAATTGTA Sequence 232

TABLE 1 42/467

AATACAAAAANATTGGCGGGGTGTGGTGGCAGGTGCCTGTATTCCCAGCTACTTTGGAGG CTGGGACGGGATAATTNCTTGAGCCCCGGAGGCGGGGGTTTCCGGTGAGCCCGGGATTGC GCCCCTTGCACTACAAGCCTGGGGCACANAAGCGAGGACTNTGTCAAAAAAAAA Sequence 233

Sequence 234

Sequence 235

Sequence 236

Sequence 237

TGTTNACCTTTGGGATTACACAATACTTGCAATCCAGCTCTGCCATGGGGGACATCATTA CACAAAGCACTCCTCACCAGTAGTCAGATGGCACTTGATAGCTACAGGCATGTGAATATT CTTTTACTGTCAACTTTTGTTGTGATTTCACCTAAAATATGATAAGCTCCTTGAGGATAA AGGCTAAGTCTTACTTCTTCGTATTTCTGGTAACCGCTTGTACCAAACACCTGCCAAGCA TTGTTGATTGCACCTATGAGGAGGTGAGAAAGTGCCAGGCCGTCATGCCCCTCTATACAA

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Sequence 238

Sequence 240

Sequence 241

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Sequence 242

Sequence 244

Sequence 245

TTCCGTACCTAAGAATTGTACCCTTTCATAACAGCACCACTTGGATATGTAGAAAGAGTT
TGTTGTGAGATCAGATGTAAAACAAATAAAAGTTATTCGTGAAATGATATGGAAGACTGG
GATTAGAAACTGTGGCATTCAAGAAGCCAGTTAAGCTGTTCTCAGAATTGACAGAGATTC
TAGAGATGGTGTAGTGCAGATGGTGTAGTGCAGGGATTCTCAGCCTCACTGCACATGGTA
ATCTCATAGGAAAATTTTAACAAGGACAGATGCAGAAATTCTTATTAAACTGTCAGGACT
GAAGTCCAGAGGTCACTATATTTTAAAAAAGGTCTGCAAGTGATTGTAACATGCATCTATG
GAGGAAAACATCANCGTAGGAGAAAAAAGGGAAAAGCAACTGGAGTAAAGGCTCTGTC
TTGAGCACTGTGCTGGCTCCTGTCATTCTCCATCTTTTTTATCTTCATAGTAAGTGAGA
TGGGTTTGACAAATAGGGA

Sequence 246

GCGTCCGGNGTAACTTGAACNAAAGTATTCTCCTTCTTCTGTATATTTGTTCTCAACCCC

TABLE 1 45/467

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Sequence 247

TGTCGACCCGCGTCCNTNGTATTTATAAANATAATNCTGNTAGATAAATAAGTGATTCA
TATTTTGTCAAANCTATTTTAAAATTTCAATATTTAAAATATTNTTGAATCACTGGGTGT
CGNTAAGTGGCATCATNNATGAGATTTGATTCCATGTACCATATAATNTTAGATTGGTCC
TNTCTCACCCCTTTTAAACTCCTTCAAGCATTGCTATTACTGGGGTTGCCTTTGGGAAAA
CTTACTTCTAGATACTACCATATATCTGAAATAGTAGAGGTGGATGTTAATAAAATTCAT
AAAATNATCATGTATTACTTTTTTTGATTTACCACTGGAAGGAAATACAGNCATGTGCAA
TATAATGACCGTTTTGGTCATNGAGACCCACATGTGTGACAGTGGTCCCATAAGGATGNG
GCTGAAAANNTCCTGTTGCNGCCTAGTGACACTGTAGCCATNGNAACNCCATAGCACGAC
ACGTNACTCACCTNTTCATGGTGATGCTGGTGT

Sequence 248

Sequence 249

Sequence 250

TCGACCACGCGTCCGGGTGAACGTGGTCACCAAGGCCATGGGTACCCTGGGGGTGAGCTT
ATCCTCCTGCAGCGTCCCTGGTTCCAAACCCACCTTCGAGCTCCAGCCGACGAGGTGGA
GCTGGGCCTGGGGATCCACGGGGAAGCTGGTGTGCGCCGGATAAAGATGGCAACCGCCGA
TGAGATTGTGAAACTCATGCTCGACCACATGACAAACACCACCAACGCGTCCCATGTGCC
TGTGCAGCCCGGCTCCTCAGTTGTGATGATGGTCAACAACCTGGGTGGCCTGTCATTCCT
GGAACTGGGCATCATAGCCGACGCTACCGTCCGNTCCCTGGAGGGCCGCGGGGTGAAGAT
TGCCCGTGCCCTGGTGGGCACCTTCATGTCAGCACTGGAGATGCCTGGCATTTCTCTCAC
CCTCCTGCTGGTGGATGAGCCTCTCCTGAAACTGATAGATGCTTGAAACCACTGCAGCAG
CCTGGCCTAACGTGGCTTGCAGTCTTCATTACTGGGCGGAAAGCGGAGCCGGGTAAGCCC
CTTGCCGAGCCCCAAGAAG

Sequence 251

TABLE 1 46/467

CCGGTGAAACCTGGAGCTGAAGTGAATTCTCTTAGAGTATATTTTGAAACTGTACTAGGA CTTTAAACACTTTTGGAATTTAAAACAGCCATAAAAATTCTTGTTATACTGAAGGAGTTC CTGAGGCAGTGTGCCTCCATTTTACCACCTAAAGTTGCCATAGAGGTCCAAGGAGACAC TGCTGATAGCAGAAAGTCTTCCAGAAAGAAATTAGGCGACCCACACCAAGCATGTATGGC TTTGAGTCTTACAGATGGCTTTTTAATAGTTTAGTCTCTTAACCTAAGGAAGTTTCTGAA GTTCCGGTCAGAGAGTCTAAAAATTCACATTTTACCTAATAAATGATAATGAGGCTATTT ATCTTGTCTGTCTGGATTTTTTCACTTGACATTTAATGAAATATCCCATATTACCTATAA TTTTTATTTGAAG

Sequence 253

CCCCCGCGTCCGAGATAATGCTGTTTGCTTCCGGCCGCTGTAAATCATAGGTGAAAACC
AGTAGCANGTGCTCACTCAGTGCCTCCCAGAAGCGGTCTGCGGGTCTCAGCTGGGCTGGG
GGCAGTTTTCATTGGGCAAGGCTTGGGCTTAGCTTCGAAGCANGGGCTGGGAGAGGATGG
ATGGGGGTGTGAGAGCAAAAGAAAGACCTGGCTTTGCAGTGATGGCANCCCACGTTCAAA
TNNAGCTCACCACTGACCNGTCGNNTGACGNGCGCCAGGNGTTAGGAGACTGNAACTGN
TTNTGNGTNNNGNNTCCGGNCGTNCATNNNNNCTGCTCAGCATACANANCCTNTTNCTNA
TCNTAATCCTCATACNCATGNCTGNNNACTNTACACTGTTCTACTTATCAATGACAGGTC
AAAAGTGTTATCATNTGTGACNTAGAATGAGTGAAAAAATC

Sequence 254

Sequence 255

Sequence 256

TCGACCCCGCGTCCGATTTGATATAAATAGTTATGTTACTCATATAGAAATCTCTTCCCC ATTACACACACACACATTTATCTATGAGTGGCTTATAATTGCAAATAAGATGTAAATC ATGCTCATGATCATTGTCAAAATTGTGAAAGATTTTTTTCTATACCTCTTTTAGGTTTGT

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Sequence 257

Sequence 259

CTGGTACCTGCGAGTCGCTGCAGCAGCTGTGGCAATTGTCACCTTCATCCAGGCCCATCC
CGCTTTGAGGGCCTAGAGAGAGTGGGCCAGAGGTTAACCCCCGATTCATCTGCCTCCCA
CGCTGGGCATCTGGGTGTGCCAGGGCATTCCCCCGCTGGTCAGACAGGTTTTTGGGCCAG
GGCGGGGCTGACCAGGGTTAATTAGAGGGAACTGGCTAGGAGAGCTGGGAGGGGGCTG
GGCAGAGTCCAGGCCTNCAGAGCCCCTGGGACACAGCAGGTGTGTGCTGCCATGGGCCGG
GGCTTGAACTCTGCCAGACTCAGGCGCCAAAAACGGCGCTTGCGACCTCAGGTCCAGAAG
CCCCGGCAGCAAGCTG

Sequence 260

Sequence 261

TABLE 1 48/467

GATAAAAATCTGGAACTTCTAGATCTGACCTTCATGCCTTGTCTTTTCTATGGTACTTAT
TCTTTCTGTCTCCTTCTCATTTTGGATTGGGCTTATGAGAGAAATCTTGGGGTTGATCTT
CCAGCTCACTAATTTGATATTCATTTGTGTCTCTTCAGTTACTTAGCTTGCCTGAAAACT
TTTTTTTTCAGCAATTGTGTACTTAATTTTCATA

Sequence 262

Sequence 264

Sequence 265

Sequence 266

Sequence 267

TABLE 1 49/467

AGAGCAAAAACCTATATATAAAGCAATTTTTAAGATTTTGGTTCTATAAGGGTAGAATGT TCGATCCATTAGTGTATTCCCAAAGTCCTATACACATGTCAAGATCGGGAAAGCTCACAC ACACAATAATGCCCAAG

Sequence 268

Sequence 271

ACCGCGGNGGCTTCATGCAAGCTGTGGGCATGGNCAACGATCACGAAAATCATTNTTCCT
TTAAATAAAATACAATCCTATNNAAAGGAGTNCTTCCATGAGCAACAATCAAATACGTGC
TTATGCTGCGATGCAAGCAGGTGAACAACTGGTTCCTNATCAANTTGACGCAGGCGATTT
ACAAGCCCATCAAGACGAAGTCAAAGTTGAATATTGTGGATTATCATTCAGATATTTC
AAGTGATTAATAATGATTGGCCGATCATCTACTTATCCTGTAGNCGCAGGTCATGAAATC
ATTGGAACCATCACTGCTCTTTGGTTCATGAAGCGAAAGGACTCAAAG
Sequence 272

Sequence 273

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Sequence 274

CCCTTAGCGTGGTCGCGGCCGAGGTACNAAATTATGACTGTTTTAGCTCCAGGAACAGAT
TTAAAAGTAATTGAAGACGTTTTAAAATCTGTTTTTGATGCTAAGAACATCGAAAAAATT
GAAAAACTTGAAAGAACAGAGTTAGCATACNAAATTAAAAAACACAAACAAGGAATTTTT
GTTTTAGCTAACTTAAAATCTGAGGAAAGTTTAATCGAAGAATTTGTCAGAAGAGTAAAT
ATTCTCAAAAAACAAGTTTTAAGATTTTTAGTTATTAATCTAGATTCTGTAAAAAACCA
CACAAACTTTCAGACCTAGAAAAAATGATAAACACAAATTTTTCTCTTCTAAAAAACCA
ACAACTTCAACAGAAGAAGATTCTTCAAAAACCAAATTTTGTCAAAAAACCTTTTGTT
AAAAAATCAGAAGAAACAGATTCTTCAAAACAAATGAACAAAGGACAAAGTGCTAAGAAA
ACCCAAAAACTGTAAAACCAGCAAAAGATTCTA

Sequence 275

Sequence 276

CCCTTTCGAGCGNCCGCCCGGGCAGGTACGCGGGGAAATGCAAAAAAATCAAATCAATTT
AATAGAATACATCAGAGATGTTAAAGATTTCCCAATTGAAGGGATTGTATTTAAAGATAT
TTCACCACTTTTAGCAAATGGAGAAGTGCTAAATTACACAATTAATCAAATGGCTGAGTT
AGCTAAAGATGCAGATGTTATTATAGGTCCAGACGCAAGAGGTTTCTTGTTTGGGACACC
TACTGCAGCTTTTTTAAAAAAACCTTTTATTATGGTAAGAAAACCTAAAAAATTACCAGG
AGACGTTATTAGTTTTGAGTATGATTTAGAATATGGTAAATCAACTCTAGAAATCCAAAC
TAATATGTTGAAAAAAAGGCCAAAAAGTAGCAATTATTGATGTTTTAGCTACTGGCGG
AACAATGAAAGCGATTATTAACTTAATCGAATCTCAAGGTGCTGGTTGNTCATAAAGTAA
TCTTTTTACTTGAATTANGATTTTTAAACCGGAATTGAAAAACTTAAAA

Sequence 277

Sequence 278

CCCTTAGCGTGGTCGCGGCCGAGGTACAAGATAGTNNTCTCAGTAAAAGGTCTATTATCT
AACTTGCCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACTGCCATAATGCCGTGCA
CAGCTTGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAGTTCCTCAGC
AGGCCTGGCTGAAGGCCCAGGAGGGAAGGAAATATAAGANCCAACAATAAAAATAGCACT
AGCAATAANAAGAATGCCATCCCATGGAGCACACCATAAT

Sequence 279

CCGAGGTACTAAACTCTNTTTAATGNNCTAACGTCATATTTTTTAAGTTTTTCAATTCCG TTTAAAAATCCTAATTCAAGTAAAAAGATTACTTTATGAACAACAGCACCTTGAGATTCG ATTAAGTTAATAATCGCTTTCATTGTTCCGCCAGTAGCTAAAACATCATCAATAATTGCT

TABLE 1 51/467

Sequence 280

TATTTGGTGAAGATCAGCGTTATCAGCATTTTCTACGATTAAACGCTGGCCATGCTTTGA CTGATGAAATCCGCCAAGCTATTCAGCAGTTGGCGGATTGGGTCAGAGAAAGTCTCAAGT CGAAATTGAGTTAGTCGAAGTCTGCTTTCAATACGATGCGATAACGTGCTTGACCTGAAT GAAGTCGCTCAATGGCATCGTTGAGCTGTGACATAGGATAGAGTTCAATTTGCGGGGCGA TATTTTACGTGCTGCAAATTTGAAGAAGTTGACGAAGTGCTAAAGGAGAACCCGTCGGT GAACCTGTTACTGATTTGGCACCATCAATCAAAGCACCCGACTGAAACTGGGAATAGGTT CTAAAAGTCAGACCTAGAAAAATG

Sequence 281

Sequence 283

Sequence 285

CGTCCGTNAGGCCTGTNCTTACGGCTGGGTTTAGAAACCAGCCCATTCAGAAAGACTGAA TCAGAACATGGATNAAGTGAACTNATTCTAAGATGACTCGNNTATCCATGTNGATTAATC

TABLE 1 52/467

TNCTGGNTCATAATAGGCCTCTTCCCTTTGATTGAAGGGTCACGTNTAAGTATANAAAAC ATAAAACTGTAAGGTAGAGGAAGCGAAGGATAGCTTNGTATTAATGTTGCGTTAAAGCTT CAGAGACAAGAACAACACTCCTCCCACGTGACAGCATTTGAATAGGAGGCGGNGGGT GCNGCAGCCTGGGCAGCTTCAGTCCCGATTTACAATAAAGTACCTTGNGNGTNATTAGTT CTTAAATGTTTATTTAGAAATGGCATTGATGTT

Sequence 286

Sequence 287

Sequence 288

Sequence 289

CGTTCCCCCCGGGT

Sequence 290

TABLE 1 53/467

AAGACCCGAA

Sequence 291

TCTTGCAGACTCAAGCTCCGCGCGCAGCCGCTCCTGGTGCGGGCCCACAGCAGCCTGGGCCCCGGNTCGGCCCCGGAGCCCCTGGCCTGCGACGACTGTTCCCTTCGATCGGCCAAATCCCCCTTCAGCCTCCTGGCGCCCATCCGCAGCAAGGACGTTCGCAGCAGGAGTTACCTGGAGGCCAGCCTNCTGGCCAGNGGGGCCCTGCTGGGGGCAGACGAGCTGGCCCGCTACTTCCCAGACCGGTACGTGGCGCTCTTCGNGGCCACCTGGAACATGCAGGGCCAGAASSequence 292

NGGCCGCCGGGCAGGTACTAAACTTTAATTAATGAGCTAACGTCATATTTTTTAAGTT
TTTCAATTCCGTTTAAAAATCCTAATTCAAGTAAAAAGATTACTTTATGAACAACAGCAC
CTTGAGATTCGATTAAGTTAATAATCGCTTTCATTGTTCCGCCCAGNTAGCTAAAACATC
ATCAATAATTGCTACTTTTTTGGCCTTTTTTCAACATATTAAGTTTGGATTTCTAGAGTTG
ATTTACCATATTCTAAATCATACTCAAAACTAATAACGTCTCCTGGTAATTTTTTAGGTT
TTCTTACCATAATAAAAGGTTTTTTTAAAAAAGCCTGCAGTAAGGTGGTCCCAAACAAGA
AAACCCTCTTTGCGTCTGGGACCTATAATAACCATCTGCATCTTTAGCTAACTCAAGCCC
ATTTGATTAATTGGNGTAATTTAGCACTTCTCCATTTGCTAAAAGGTGGTGAAATAATCT
TTÀAAATACAATCCCTTCAAATTGGGGAAATCTTTTAAACATCCCCCGGCGGTACCTCGG
GCCCGCTTCTAGAACTAGTGGGATCCCCCGGGCCTG

Sequence 293

GCTCCCGCGGTGGCGGCCGCCCGGGCTGGTACGCGGGGAAATGCAAAAAATCAAATCAA
TTTAATACGAATACATCATGAGATGTTAAAGATTTCCCAATTGAAGGGATTGNNTTTAAA
GATATTTCACCACTTTTAGCANATGGAGAAGTGCTAAATTACACAATTAATCAAGTGGCT
GAGTTAGCTAAAGATGCAGATGTTATTATAAGGCCCAGACGCCAAGAGGTTTCTTGTTTGG
GACACCTACTGCAGCTTTTTTAAAAAAAACCTTTTATTATGGTAAGAAAACCTAAAAAATT
ACCAGGAGACGTTATTAGTTTTGAGTATGATTTAGAATATGGTAAATCAACTCTAGAAAT
CCAAACTAATATGTTGAAAAAAAGGCCAAAAAGTAGCAATTATTGATGATGTTTTAGCTAC
TGGCGGACAATGAAAG

Sequence 294

Sequence 295

TATAGGGCGAATTGGAGCTCCCCGCCGNGGTCCCAAATGGAAGTGTGAAAACCANGGCC CATCCCCCNNTTTTNTAGAGGGGTGGTAAAAAATAAACCCANANATCAAGGGAGAAAGG AAAAGGATGAAAGGACAAACTGCCAAAAAAATTTNCCCAAAGTGGCGACTTTTTTAANTN TGGGAGCCAGAATTCTGAGGGCTTTGCATTGTCTTTGCAATTCNCTCAAGGAGCCTGAAA TTGAAAAAAAATGCCAACAAGGCCAAATNAACTACTTTTTAGGAGGGGGTTTTGGAGGTC TTGGGAAGCCTCATTCCCNTTCAACCNNTCNAATTCTGGGAATGGGGGAAATGGAAAAATTNCT NCACCCAAGGTTGGGTACCACAAAAAATTTGTAATGGACTGGTATTGGCAAAAATTNCT NCACCCAAGGTTGGGTATTCAAAAATATTGTAATGGACTGGGTATTGGCAAAAAAGG

GGCGAATTGGAGCTCCCCGCGGTGGCGGCCCGAGGTACAGGTGGGTCCCTTTTCAGAGGT TGGGCCTTCTAGACCTCACCTGTTCTCACTNCCCTGGTTTAAATTCAACCCCAAGCCATG

TABLE 1 54/467

GCCAATGGCCAAATAATAGAAATTGGTTCCCTACCCAGCTGGACCAGGGGAGGAGGTCT TGTGCAGTTTCTTGACCACTTTGTTGGTTGGACCATNGGCTTAAATACCAATGGGGTATT CGGCTTGAGACCTAAAGTTTGTAAGAAAATTNAACCAAAATGGTGCCTGCTTGGGTTAAA AATGGGCTACCACCTCAATCTGGACTTCAATTCTTTTAATTCTAATTTTAAGTTTGGGTT TTGGTATTCTTTGGCCTAAAGGTGGCGGTAGTCCCAACCTCTTTGGGTANTTACCCCTTC CTAAATAGGTCAATACCTAGGTAGGTCAATACCTCCCTGGGTGGTAAGGNGGTATTTCTT CTTAAAAAAGCCTTTTTAAAA

Sequence 297

Sequence 298

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGNCAGGTACGCGGNGAAATGCA
AAAAAATCAAATCAATTTAATAGAATACATCAGAGATGTTAAAGATTTCCCAATTGAAGG
GGTTGTATTTAAAGATATTTCACCACTTTTAGCAAATGGAGAAGTGCTAAATTACACAAT
TAATCAAATGGCTGAGTTAGCTAAAGATGCANATGTTATTATAGGTCCAGACGCAAGAGG
TTTCTTGTTTGGGACACCTACTGCAGCTNTTTTAAAAAAAACCTTTTATTATGGTAAGAAA
ACCTAAAAAAATTACNAGGAGACGTTATTAGTTTNGAGTATGATTTAGAATATGGTAAATC
AACTCTAGAAATCCAAACTAATATTTTGAAAAAAG

Sequence 299

Sequence 300

Sequence 301

Sequence 302

AGGTACTTTGATATCTNCGCCCTCTCGTGTGTTCCTTGTGGNGNTAACCAGAGGCAAGAT GCCCGAGGAACTTCATGTGTATGTCTACCAGGATTTCAGATGATCTCTAATAATGGAGGA CCTGCTATTATTTGTAAAAAGTGCCCAGAAAACATGAAAGGTGTTACAGAAGATGGCTGG AACTGCATTTCTTGCCCTAGTGACTTAACTGCCGAAGGAAAATGTCACTGTCCCATTGGC CATATTTTAGTGGAAAGAGAGACATTNATGGAACATTGNTGNCTCAAGCAACTNGNGAGCTC

TABLE 1 55/467

TGNGATGGAAATGAAAACTCTTTTATGGTAGTAAATGCTTTAGGAGACAGGNGCGTNCGA TGTGAGCCAACATTTGNTAATACCAGCAGGTCCTGTGCATGTTNCGAACCTAACATTTTA ACAGGGGGATTATGTTTCAGNAGCACAGGGAATTTTTCCTTGTACGTANAATTTCACCTG CACGTTATGGAGAAGTTTGGCAT

Sequence 303

Sequence 304

GCGGTGCCGAGGTACCTTNTCCGAATGCACCTTNAAAGCGGGTATTAGCCTATACA GGCTGTTTTAGTCGAATGCAGACCATCAAGGAAATTCNNGAATATCTATCTCAAAGACTG CGCATTAAAGAGGAAGATATGCGCCTGNGGCTANTCCANAAGTGGAGAANTACCTTACTC TTTCTGGGNTGATGAGGAATCATAAATCTGGAATATTTNGAAAATCCAGGATGAACAACA C

Sequence 305

GCNGNCGCGGGGAAATGCAAAAAAATCAAATCAATTTAATAGAATACATCAGAGATGTTA
AAGATTTCCCAATTGNNGGGATTGTATTTAAAGATATTTCACCACTTTTAGCAAATGGAG
AAGTGCTAAATTACACAATTAATCAAATGGCTGAGTTNAGCTAAAGATGCAGATGTTATT
ATAGGTCCAGACGCAANGAGGTTTCTTGTTTGGGACACCTACTGCAGCTTTTTTAAAAAA
ACCTTTTATTATGGTAAGAAAACCTAAAAAATTACCAGGAGACGTTATTAGTTTTGAGTA
TGATTTAGAATATGGTAAATCAACTCTAGAAATCCAAACTAATATGTTGAAAAAAAGGCCA
AAAAGTAGCAATTATTGATGATGTTTTAAGCTACTGGCGGAACAATGAAAGCCGATTATT
AACTTAATCGAATCTCAAGGNGCTGGTGNTCATAAAGTAATCTTTTTTACTTGGAATTAG
GGATTTTTNAACCGGAAATTGGAAAAA

Sequence 306

ATAGGGCGAATTGGAGCTCCCCGCGGTGCCGCCCCGGGCAGGTACGCGGGGCAATTA
TGAAATTATTGCAGAAAGAAGATTCACTCTCACCTGATGAATAAGTGTTCATAGGTNAAG
GCTACAAAATACTAATTTGTTATTTTTAATCAATAATTTTTTGTTTTGCTGAGAAAGTG
GATTTACCACTTTTTTATTTTTTAATCCAAGGAGGAAAAATTATTTCCAAACCAAATCCT
AAAAATTTTTCACGTTCTAAACCAGTTCAAGAACATTGAGTAAACAGAAATATTCCATTT
GTCAAAGTTTTTCTTATCGGCTCAGATAATGAAAAAATTGGGATAATTGAAACAAGAGAA
GCTATTGAAATGGCAAAAGAACAAAA

Sequence 307

CGAATNGGAGCTCCCCGCGGTGGCGGCCGAGGTACGCGGGGGCAGCAAGCGGACGTGAGC
GATAATGGCGGATATGGAGGATCTCTTCGGGAGCGACGCCGACNGCGAAGCTGAGCGTAA
AGATTCTGATTCTGGATCTGACTCAGATTCTGATCAAGAGAATGCTGCCTCTGGCAGTAA
TGCCTCTGGAAGTGAAAGTGATCAGGATGAAAGAGGTGATTCAGGACAACCAAGTAATAA
GGAACTGTTTGGAGATGACAGTGAGGACGAGGGAGCTTCACATCATAGTGGTAGTAAA
TCACTCTGAAAGATCAGACAATAGATCAGAAGCTTCTGAGCGTTCTGACCATGAGGACAA
TGACCCCTCAGATGTAGATCAGCACAGTGGATCAGAAGCCCCTA
Sequence 308

TABLE 1 56/467

CCGCGGTGGCGGCCGCCCGGGCAGGTACTGACCCTCCTTGATGGTTTACTTTGCAAGCTA
TGGTGACCTCCGCAAGTTGTGTCTGGGCCCATCCAGGGCTCTGACTAATTGTATTCAAAT
CAAGGCAGGAGCGGGCCAGCTGGCGTTGACTTAACCCAGCCATTTTATAAGCCTCCCGAT
CATTTTTAAGCCACTCTAAGTCGTGTAGTAGGATCTGGTCAGAGTTATGTATACTCTGAT
GGGCATGTGCTGTGTCGTCTAAAATGTCCAGAAGTTCTGAAACACTTTTAGATCTTCCAG
AATTTCTTGAGGAAGTCTGCCTAAGTAACTGATGCACATCAAGTTCATCACCGGAGGAAT
CAAAAGAATTTCCATTTTCTATTTCTCTACAGAAAAGAAAAGGATCTTCCTTTAAGATGG
AAATATTATTTCTCTTC

Sequence 310

Sequence 311

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGNCAAGGTACCTGACTGTGGC TCANATCTGCGTCGCAGCAGCAGAGAAAATCACTCCATATCCGATGAGAGGAAGGGT GGCACAGANATGGTGTCTACAATTAGAGACATTTCTGACTCCACCTTAGCCTAAGCAAAC TTTATATACTGAGTAACATTTGAAGGTTGTCTTTTAATGGTGGGGGGGTGNTTTTTCCTTT TTAAACTACAGT

Sequence 312

CCAAAANGGGNCCTGGGGCGTGGTCACGGCCNAGGTACAAAATTATGACTGTTTTAGCTC CAGGAACAGATTAAAAAGTAATTGAAGACGTTTTAAAATCTGTTTTTGATGCTAAGAACA TCGAAAAAAATTGAAAAACTTGAAAGAACAGAGTTAGCATACGAAATTAANNAGCACAAA CAAGGAATTTTTGTTTTAGCTAACTTAAAATCTGAGGAAAGTTTAATCGAAGAATTTGTC AGAAGAGTAAATATTCTCAAAAAAACAAGTTTTAAGATTTTTAGTTATTAATCTAGATTCT GAAAGAGGGAATGCACAAAACTTTCAGACCTAGAAAAAATGATAAACACAAATTTTTCTCT TCTAAAAAAACCA

Sequence 313

AATNGGGCCTNGCGTGGTCACGCCCAGGTACNAAATTATGACTGTTTTAGCTCCAGGAAC AGATTAAAAGTATTGAGCNTTTTAATCTNTTTTGATCTAAGACATCGAAAAATTGAAAACT TGAAAGACAGAGTTAGCATACNAATTTAAANGCACAACAGGATTTTTTGTTTTACTAACT TAAATCTGGGGAAGTTTAATCNAAGATTTGTCAGAAGAGGGATTGCNCAAAAACAAG TTTTAAGATTTTTAGTTATTAATCTAGATTCTGAAAGAGGGATTGCNCAAAACTTTCAGAC CTAGAAAAATTGATAAACACAAAATTTTTCTNTTTTAAAAAA

Sequence 314

NGGGCCTNGGNGTGGNNACGANCCAGGTACTTTTACCAAAGAATCTACTAGAACTCTCTG
CTATTCAAAACAAAGAGCTCATACTTGTTGGAGTAGGGAAAAAATTAGAAATTTGACCAA
AAGATAGATTCAATCAACTACAAAGTCAATTCCAAGATGCTGNTAACATCGAAACTCTTG
AAAAAGAACTATTANAATCTGGAGTTGAACTTTAATGGATCATATACCTGNTTTGCTTGA
TCAAGCGGATTGNTCAGCTTAATATTAAAGAAGATGGNATCTATTTAGATCTTACTTTAG
GACGNGGNGGNCATTCGAGNCAAATTTTAAAAAAAACTTACTA

TABLE 1 57/467

CCCTTTCGAGCGGCCGCCCGGGCAGGTACTTGTCCATAATTTGTGAATATATAACTAAT
TTTTCTTTTGAGTATTCATTTACTAACTCATAAGCTGAAAAGCTTTGAGCTTGATTCATT
CTCATATCCAAACGAGCTTGTTTGTTGTATGAAAATCCTCTATTGGCTTGATCTAACTGA
GGTGAAGATACTCCTAAATCAAGTAATACACCATCTACTTTGTTGATTTGAAGTTTTTT
AGTTCTTGATCAAAATCTTTAAAATCAGATCAAATAAATTCAATATTTGAAGAAATTTTT
AAGAGTTTTTCTTTTGTTTGTTCAATTGCTTGTTTGTTTATCAAAGACTA
Sequence 316

Sequence 317

Sequence 318

Sequence 319

CCCTTAGCGTGGTCGCGGCCGAGGTACGCGGGGCAATACGTAGAGATAATAACAGTTTTT
TAAAAAACTTAATATTTGTTATTGAATGTATATTTTTGAGTATTGCATCTTTTCTATACT
AATAAGGAGGTGTAATTTGAACGCTTTTAGAAAGAAAAAAGAAGAAATTAGTGCAAGAAAT
TAAAGATTTGATTAATTCTTCTTCTTCATTAGTTATAGCTGAATATCGTGGATTAACAGT
TGCTGAAATTGAAACTCTTAGAAATGAAGCTTAAAGAAGCAGGTGTTTTTGTAAAAAGTTT
ATAAAAATAGACTATTTAAAATAGCATCTAAAGAAGCAGGTTTCGGAGATTTAGAACAAT
CACTAGTTGGTCCAAATTTTTTTGCTTTTTGGTTCTACAGATGCANTAGCTCCAGCTAAAA

Sequence 320

Sequence 321

TABLE 1 58/467

TGCCTGGAGTTTGAAATACATGTCTCTTTAGTTTCTTTTGCACATGCTACATTGTGCTTT
AGACCGGAGATAATACAGTGACTTTACCTCACAAATCATATTCTGTCAACACACAATCTAT
GAATTTAGTTTATTTAAAATCAGAACAATTTCCTACAAAATTTTTCTGGAAAATAGACTC
CTAACAGACCTACCAGAATCATGCTTAAAGGGCTCCCTTGACACTTATTCTATACTGAAG
GATAAATTTTAAAAAAAT

Sequence 322

Sequence 323

GCGGTGGCGCCCGGGCAGGTACAAGGTAAAGCAAGAGCTGGCTCTCTACGTTCACC
AATTTTTGTAGGTGGTGGTCGTGCATTTGGGCCTACAAATAAAAAATTACAAAATTAA
ATTAAACAAAAAAGTTCGCAAATTAGCTTTTGCCTCAGCTTTTAAGTCAACTTGCTCAAA
ATAATCAAGTACCT

Sequence 324

NNCTTAGCGTGGTCGCGGCCGAGGTACGCGGGGAAATGCAAAAAATCAAATCAATTTAA TAGAATACATCAGAGTTAAAGATTTCCCAATTGAAGGGATTGTATTTAAAGATATTT CACCACTTTTAGCAAATGGAGAAGTGCTAAATTACACAATTANNCAAATGGCTGAGTTAG CTAAAGATGCAGATGTTATTATAGGTCCAGACGCAAGAGGTTTCTTGTTTGGGACACCTACTGNAGCTTTTTTAAAAAAAACCTTTTATTATGGTAAGAAAACCTAAAAAAATTACCAGGAGACGTTATTAGTTTTGAGTATGAGTTTAG

Sequence 325

Sequence 326

CCCTTTCGAGCGGCCGCCCGGGCAGGTACTTGTCCATAATTTGTGAATATATTAACTAAT
TTTTCTTTTGAGTATTCATTTACTAACTCATAAGCTGAAAAGCTTTGAGCTTGATTCATT
CTCATATCCAAACGAGCTTGTTTGTTGTATGAAAATCCTCTATTGGCTTGATCTAACTGA
GGTGAAGATACTCCTAAATCAAGTAATACACCATCTACTTTGTTGATTTGAAGTTTTTTT
AGTTCTTGATCAAAATCTTTAAAATCAGATCAAATAAATTCAATATTTGAAGAAATTTTT
AAGAGTTTTTCTTTTGTTTGTTCAATTGCTTGTTTGTTCTTTATCAAAGACTA

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TABLE 1 59/467

TGTGTGAGGCCACAACTGTCCCATTATGCATATCANAAACAGAAATTTGTTGAGGATAAT TTTGGATATTCAGCAGNGGCTGNGAAACTGGATTTGAATTACCGGGATACATGCATGCTT CTTGGTT

Sequence 329

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Sequence 331

Sequence 332

Sequence 334

CCGGGCAGGTACTAGGAGATATTGATTCTAGTCAATTAGGCATTGTAGACTGTCATGACC ACTTAATAAAAAATTATGGACCTGAAGCTCACGAGCATCCAGATTTTATTATGATGTCAA AAGATGCTGCAATTAAAGAAATGAATGAATATGTAGCAAAAGGAGGAAAAACTGTTGTTA

TABLE 1 60/467

CAATGGACCCTCCTAACGTTGGGCGTGATGTTTATCAAATGTTAGATATTGCAAAGAAAT TAGAAGGAAAAGCTAACATTATTATGGCAACTGGTTTTCATAAAGCTGCATTTTATGACA AAGGTGCTTCTTGACTTGGCTCCAACAGATAAAATTGNAAAAATGGTTGTAGCTG AAATCGAAGAAGGAATGGATGAATATAACTACAGCGGACCAGTTGTAAAAAAGATCTAAAT CCAAAGCCGGAATTATTAAAGC

Sequence 335

CTCCCGCGGTGGCGGCCGAGGTACCGCGGGGAAATGCAAAAAAATCAANNCAGTNNANT CNAATACATCACAGATGTTNAAGATTTCCCAATTGAAGGGATTGTATTTAAAGATATTTC ACCACTTTTAGCAAATGGGAGANGTGCTAAATTACACAATTAATCAAATGGCTGAGTTAG CTAAAGATGCAGATGTTATTATAGGTCCAGACGCAAGAGGTTTCTTGTTTGGGACACCTA CTGCAGCTTTTTTAAAAAAACCTTTTATTATGGTAAGAAAACCTAAAAAATTACCAGGAG ACGTTNTTAGTTTGAGTATGATTTAGAATATGGTAAATCAACTCTAGAAATCCAAACTA ATATGTTGAAAAAAAGGC

Sequence 336

- Sequence 337
- CCGCGGTGGCGGCCGAGGTACCAATAATAGCAACCCTGTGATTTGTCCAAGTGCCCGGGA GTGGAGGCCATCCTGACAACAGCTCTATGATTTTCTATGCCAATGACACAGGAGCCCAAC AGTTTGAAAAGTGGTGGGATAAGTCCAGGACAGTCCCCTTTTATCTTGTAGGGCTCCTCC TCCCACTGCTCAATTTCAAGTCTCCTTCATTTTTTTCAAAATTTAATATCCTAGGCACAG TGTCTGTCCTTTATTTGATTTTCCTTGTCACCTTTAAGGCTGTTCGCTTGGGATTTCATT TGGAATTTCATTGGTTTATACCAACAGAATTTTTTGTACCTGCCCG
- Sequence 338
- CCGGGCAGGTACCTGGAAGACTTCTCCACCTCGGGGGCCTGGCTGCCTCACAGGTATGAA GACAACCACCATAACTGCTACTCTTACGCACTCACGTTCATTAACTGCGTTCTGATGGCA GAAGGTAGACAGCAACTGGACAAGGGTGAATTTACGGAGAAGTACCT Sequence 339
- ATAAACTGCGGGATCTCAATGGCTTCTATGATCGTATTGAGGCAGTAGTTCCCACACTCT GCCCGGTGCCAGCATGAAAGAGAACAGGGAGAGTCAGCCTTTCACAGTCCTTGTCAAATC CCAATTACTCTGGTTGCAGATCACTTGAAGCCTGCCTTGTTTCTCTCACAAAGCTCTGCC CGAGAGTCCAGCCCCGCGTACCTGCCCG

Sequence 340

GCGAATTGGAGCTCCCCGCGGNGGCGGCCGAGGTACAAGATAGTCATNTCAGTAAAAGGT CTATTATCTAACTTGCCAAACTTGTTTANNGAGAGCCCTAAGGAACTAAAACTGCCATAA TGCCNTGCACAGCTTGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAG TTCCTCAGCAGGCCTGGAGGGCCCAGGAGGGAAGGAAATATAAGAACCAACAATAAA AATAGCAATAGCAATAAGAAGAATGCCATCCCATGGAGCACACCATAATTCTGGAACCAC CTNTCCCGGATCAGGCTTCCATTGCTCACGATGCTCACGCTGGGCAG

TABLE 1 61/467

CCGGGCAGGTACCGCTGTGTCCGGGTGGTGGTCATGAATGCCGTGCTCCAGGTGTTCAC
AGCTGCTTCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTACGCAAATGTTGC
CTGTGCCCAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAGAGTGAGCTCGCT
GGAGGGGCAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTNTTGCCAGATGACAAGGN
GACTGCATTACACCACTCAGTATATGTGAGGGAGGGGATGTGCCTCTGGCCAC
Sequence 344

Sequence 345

Sequence 346

CACTACTATAGGGNGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTAGGA
GATATTGATCCTAGTCAATTAGGCATTGTAGACTGTCATGACCACTTAATAAAAAATTAT
GGACCTGAAGCTCACGAGCATCCAGATTTTATTATGATGTCAAAAGATGCTGCAATTAAA
GAAATGAATGAATATGTAGCAAAAGGAGGAAAAACTGTTGTTACAATGGACCCTCCTAAC
GTTGGGCGTGATGTTTATCAAATGTTAGATATTGCAAAGAAATTAGAAGGAAAAGCTAAC
ATTATTATGGCAACTGGTTTTCATAAAGCTGCATTTTATGACAAAGGTGCTTCTTGACTT
GCTTTGGCTCCAACAGATAAAATTGTAAAAATTGGTTAGCTGAAATCGAAGAAGGAATG

Sequence 347

GGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCGTAGAAGAAGAAGAAGAAATACCTAAAGAAACAGACATAGAAATCATCCCAGAAATCCCGGAAACTCTAGAGCCACTGTCCCTTCCAGATGTGCTGAGGATCTCGGCAGTTCTGGAGGACACCACAGGCCAGCTCTCTATTCTGAACTACATCATGCCCGTTCAGTACCT

Sequence 348

TABLE 1 62/467

AGATTACTTTATGAACAACAGCACCTTGAGATTCGATTAAGTTAATAATCGCTTTCATTG
TTCCGCCAGTAGCTAAAACATCATCAATAATTGCTACTTTTTTGGCCTTTTTTCAACATAT
TAGTTTGGATTTCTAGAGTTGATTTACCATATTCTAAATCATACTCAAAACTAATAACGT
CTCCTGGTAATTTTTTAGGTTTTCTTACCATAATAAAAGGTTTTTTTAAAAAAGCTGCAG
TAGGTGTCCCAAACAAGAAACCTCTTGCGTCTGGACCTATAATAACATCTGCATCTTTAG
CTAACTCAGCCCATTTGATTAATTGTGTAATTTAGCACTTCTCCATTTGCTAAAAGGTGG

Sequence 349

TCTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTAAAACAGGT GCTCCTGTTAAAATAGAAGATCTTGCAGCTACTTCTAGAGATTTAAATTCTAAACGATCA ATAGCAGCGTATCCTGTTCCGGCTTTAATAATTCCGGCTTTGGATTTAGATCTTTTTACA ACTGGTCCGCTGTAGTTATATTCATCCATTCCTTCTTCGATTTCAGCTACAACCATTTTT ACAATTTTATCTGTTGGAGCCAAAGCAAGTCAAGAAGCACCTTTGTCATAAAATGCAGCT TTATGAAAACCAGTTGCCATAATAATGTTAGCTTTTCCTTCTAATTTCTTTGCAATATCT AACATTTGATAAACATCACGCCCAACGTTAGGGAGGGTCCATTGTAACAACAGTTTTTCC TCCTTTTGCTACATATTCATTCATTTCTTTAATTGCAGCATCTTTTGACATCATAAAAA ATCTGG

Sequence 350

TAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACATTCTTCACTATCA CTGTCCTGTAAATTTAGTAGCCTTGGCTGGAAACACTGTAGTCGACATGATCTGATATTG CTTAATATTTCAGAAAGAGACAGTCTATTTTCACAATGTTTACTGGAAGCATTGGTCCGA GAGAAATTAGAAGAAAAGTCTATAGTTTGGGAAGAGCTTGAAAAACTATTCAGCATTTCA GGGTCTATCTGTTTCAGGACTGGGTCATGTTCTGTGGATATTCGGTCCATTATGACCCTT CCACCTCTGCCAATTCGCCTCCTTGCAAATCCTATACATCTTCTTGGGACTGTAAGTGTT GTAAGGC

Sequence 351

Sequence 352

Sequence 353

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Sequence 354

Sequence 355

Sequence 356

Sequence 358

GAATGGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAGATAGTCATCTCAGTAAAAGGTCT ATTATCTAACTTGCCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACTGCCATAATG CCGTGCACAGCTTGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAGTT CCTCAGCAGGCCTGGCTGAAGGCCCAGGAGGGAAG

TABLE 1 64/467

Sequence 360

CCGCGGTGGCGGCCGAGGTACAAGATAGTCATCTCAGTAAAAAGGTCTATTATCTAACTTG CCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACTGCCATAATGTCGTGCACAGCTT GAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAGTTCCTCAGCAGGCCT GGCTGAAGGCCCAGGAGGGAAGGAAATATAAGAACCAACAATAAAAATAGCAATAAGAATAAGAATGCCATCCCATGGAGCACCATAATTCTGGAACC Sequence 361

Sequence 362

Sequence 363

Sequence 364

AGGTACTAAACTTTAATTAATGAGCTAACGTCATATTTTTTAAGTTTTTCAATTCCGTTT
AAAAATCCTAATTCAAGTAAAAAGATTACTTTATGAACAACAGCACCTTGAGATTCGATT
AAGTTAATAATCGTTCATTGTTCCGCCAGTAGCTAAAACATCATCAATAATTGCTACTTT
TTGGCCTTTTTTCAACATATTAGTTTGGATTTCTAGAGTTTACCATATTCTAAATC
ATACTCAAAACTAATAACGTCTCCTGGTAATTTTTTAGGTTTTCTTACCATAATAAAAGG
TTTTTTTAAAAAAGCTGCAGTAGGTGTCCCAAACAAGAAACCTCTTGCGTCTGGACCTAT
AATAACATCTGCATCTTTAGCTAACTCAGCCATTTGGATTAATTGTGTAAATTTAAGCAC
TTCTCCATTTGCTAAAAGTGGTGAAATATCTTTAAATACAATCCCCTTCAATTGGGAAA
TCTTTAAACATCTCNGGATGGTATTCTATTAAAATTGAATTTTTTTTGGC
Sequence 365

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Sequence 366

CCGCGGTGGCCGCCCGGGCAGGTACGCGGGGAAATGCAAAAAAATCAAATCAATTT
AATAGAATACATCAGAGATGTTAAAGATTTCCCAATTGAAGGGATTGTATTTAAAGATAT
TTCACCACTTTTAGCAAATGGAGAAGTGCTAAATTCACAATAATCAAATGGCTGAGTTAG
CTAAAGATGCAGATGTTATTATAGGTCCAGACCCAAGAGGTTTCTTGTTTGGGACACCTA
CTGCAGCTTTTTTTAAAAAAAACCTTTTATTATGGTAAGAAAACCTAA

Sequence 367

Sequence 368

Sequence 369

Sequence 370

Sequence 371

AGGTACTATTGACTAAAGTCAGTTGGGGGAGAGAGAGGCGGAAGTATATTACTTTTATGC TTGGTTATACTAGAGAACAAATAGAAACTGACTAAAGAAACATTAGATCAGTGGTTCTCA GAGTATTGATATCTGGGAGTCCCAGCAACAGTCTGAGGAGGTTCATGAGTTCAGAATATT TTGATAATAACACTAAGATGGTATTTACTCTTCTAACTGGGTAGATATTTGCACTGGT Sequence 372

ACTITITITITITITITGCTCAATAGAAGTATGGAATAATTCCAGGTAATTTAAAGCATA TTITTCAATTGGTGTAAGCTGCTCCATGAAGTCAGCTAGCTCCTCTAATTGGGATGGTTC TTCATCACACGGCATGTTCTCAGAGTCTGATGACAGAGCATCAGTGTGTGGTCCCAGCAC

TABLE 1 66/467

CCCCTCCTGTGCGGACTTCTGGGCATCCTCCAGATACTCAATACTCTTGAGGGCCTG AGGAAAGTCTCTATGAAAGGTCTTGCAATTTTTGGGTGCAATGGTTTCCGTGACAGAAGGT TCCTGAGAAAGCACCACAAACTCCTCAGCTTTGACCGGGAAGCCAGCATCACGGACGCGT GGGTCGAAGCTTGACCT

Sequence 374

Sequence 375

NGCGNTGCGCTCACCTGCCCNCTTTCCANTCGAGGNAAACCTGGTCGTGCNAGGGTGCNA
NTAATGAATTCGNCCAAACNCCNCCGGNNGAGNAGGCGGTTTTGCGTNATTGGGGCCGCT
ATTCCNCTTTTCTCGCTCACCTGACTTCGCTGCCGCTCGGTCGNTCGGCTTGCCGGCCGA
AGCCGGGTAATTCAAGCCTCCACTCAAAAAGGGCCGGGTAAATTACCGGGTTTNTTCCAC
CAANGAAATTTCAAGGGGGGGGATTAAACCNCNAAGGGAAAAANGAAACATTGTNNGANNC
AAANAAAGGGCCCNNNCAAAAANNGGGCCCANGNNGAACNCNCCGTAAAAAAAAAG
Sequence 376

Sequence 377

Sequence 378

Sequence 379

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GAATTGNAGCTCCCGGGTGGCGGCCNNCCGGNCAGGTGGAAAGGTGGGTGGGAGAGG GAGGCTTATTTGTTGCTGCAGTGTAACTAAGTGAAACCTAATTCATATGACTCAAACTAA GGTATATTTGGTTAGATCTAGGTGAGTTCTACTTTAGAGGAAATCCTGGTAACTGTTGTT TGTTTGTAAGTTATAGCTGTAATTAATTTTCCCTGTATTCAAAGCCCCCAAACCCTGCAT TCAGATACTATGCATTTAGACTTCCTTAGGCAAAGTCAAGGCAACAAGCTGATGATTCTA AGCTATTATTCAAGGAGTATCTACCATCATAAAGGTGGTTTAAGTCATATAGGATAATAT CAATCAATAATACAGGGAGATGGCAAAAATTTTTTGGGNAAANCCCAATATTANCTTGGG TTTNATGACCCCCNAATCTCACACTTTGGGGNCNTATGGGAAAGGCTTTTTTTTAAGACCC GGGAGTTCAAGACCNGCCCTGGGCAACATTAAAAAACCTCCTTTNNNCCAAAANCTTTAA

Sequence 380

TAGGGCGAATTGGAGCTCCCGCGGTGGCGGCCGCCCGGGCAGGTTACAAGTCGACCCAC GCGTCCGCTTCAGAATATCCAATTCATGTGAACTACAGGAAATTATAGTTTAGATATTTT TAAATGATTTGCCTGTCACCGTATAACACAAGGGTGTCATGACCAAGCTAGATCTCTTTA CCATATCATTAATAAAAGTCAAATTTTAAATTTGTGCCCAATTTGGCTGGGTGTGGC TCATTCCTGTGATTCCAGCACTTTGGGAGACCT

Sequence 381

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTTCGACCCACGCGTCC
GCATTTATTAAGGCTTGTATATGTTCAAGATCCAGTGAAGACTGTCTTGGGCGTGTATAA
TTGATCTTAACCACAAGGCTGAGAAGTTATGTGCAGGGCTTATGATGCTACTTCCAAAGT
ATTAAATCCTCCAGAGAAGCCTGTAGTGTGGGATGCAAACTATTTTAAGTGTGACCATGA
GGTGTTTTTTTTGTGGACCATTTTAAAGCCAATGATAGGTTCTAAAGCAATCTCAACCTGA
GTTAGGTAGAATGGGTTGGTTATCTGCACTCTAGCGCCCCTTCATAGCTATTGTATTCTG
GATTTCAATTCGGCACTTTATGTATTAGCTAAAAATTTCATGACCAGATCTTTTGAAGTA
TACAAAGTAAATCTTCAAGGTGGATAGTTTATCCAAGTGTAAAATGTGTTGCACTAGGTC
AGCTTGGAATTTTGAGATGACTTTTGGCATCATTGCATACATCTGGTTTGTTACCTGCC
CGGGCCGGCCGCTCTAGAACNGTGGATCCCC

Sequence 382

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTATTGACTAAAGTCA GTTGGGGGAGAGAGGCGGAAGTATATTACTTTTATGCTTGGTTATACTAGAGAACAAA TNGAAACTGACTAAAGAAACATTAGATCAGTGGTTCTCAGAGTATTGATATCTGGGAGTC CCAGCAACAGTCTGAGGAGGTTCATGAGTTCAGAATATTTTGATAATAACACTAAGATGG TATTTACTCTTCTAACTGGGTAGATATTTGCACTGGT

Sequence 383

TTAGGGCGAATTGGAGCTCCCCGCGGTGCCGCGCGAGGTACATATCTGCATATACACCAT
TAATTTTACATCGTTGAGGTAGCCAAAACTGCTCGTAAGTGGGCTTTTATTAAATAATAT
AATGTTCTTAATAGAGGAAAAAGGAATTGAATACATTTTTAAAAAACAAAATAACAAAACC
AATCCATTGTCCCACAAAAGAAAATCAGTGGAGACAAAAGCAGTTTAATTTGCTGGATTC
TTTTGTGGCTTATTTTTTGAGTATTATTTACAAAATGTTAGACTAATTTTTAAGCAATAT
TAATAATAAGCAACATACAACTCCAAGAATAATAAAATAAAATAAAACTGCGGACGCGT
GGTTCGAAGCTTGCTCGNNGGGGGCCGGGNCGCTTCNAGGCCCNCCCGGGCAGGTACCCA
GTNATCACATAAATTCTGCAATCATNTGGNTATTNAGCTTNACNTGNTTTTTTTATTTGN
NGAANTTGTTGTTGTATTCAG

Sequence 384

ACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTTACAAGTCGACC CACGCGTCCGCTTCAGAATATCCAATTCATGTGAACTACAGGAAATTATAGTTTAGATAT TTTTAAATGATTTGCCTGTCACCGTATAACACAAGGGTGTCATGACCAAGCTAGATCTCT TTACCATATCATTAATAAAAGTCAAATTTTAAATTTGTGCCCAATTTGGCTGGGTGTGGT GGCTCATTCCTGTGATTCCAGCACTTTGGGAGACCT

Sequence 385

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Sequence 388

Sequence 390

Sequence 391

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Sequence 392

Sequence 394

Sequence 396

Sequence 398

Sequence 399

CCGCGGTGGCGGCCGAGGTAGCTTGAGTCGACCCACGCGTCCGTTCAGATCCGTTTCAGA

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AACGTGAGTCTCTAGCTCAGGAGATTTCCACAACTGTCCTTAGTAACCTGATCTTATTCT
CATGTTTAACCTTGGCAGTGGGAAGTTCTTCCTGGTATCCTGCCTAATTTACTGGAGTTG
GCATTAATGCCATTTCCCCCTAAGGCGTGGCTCTTGGACCAGTATCACCTGAGAATTTGA
TAGACATAGACCCAGAGTTACTGAGGCAGGTGCTCTGTTTTGGGGACCAGCAATCGGTGC
TTTAGCAAGTTCTTTGGGTGATAGGGTTTGGAAACTACTGCTCTAAAGCATCATCTGTTT
TGACTTTGCCATGCACAATCTGAACTCACTCCCGTGAGGCCCTGCTCCTGATACTTTAAA
TCGTCCTGTCTCTTTTTCTGCCTCTCTGTGGAG

Sequence 400

Sequence 401

Sequence 404

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Sequence 406

Sequence 407

Sequence 408

Sequence 409

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGCCCCGGGCAGGTTACAAGTCGACCCAC GCGTCCGCTTCAGAATATCCAATTCATGTGAACTACAGGAAATTATAGTTTAGATATTT TAAATGATTTGCCTGTCACCGTATAACACAAGGGTGTCATGACCAAGCTAGATCTCTTTA CCATATCATTAATAAAAGTCAAATTTTAAATTTGTGCCCAATTTGGCTGGGTGTGGC TCATTCCTGTGATTCCAGCACTTTGGGAGACCT

Sequence 410

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGACCAGTGCAAATATCTACCCAGT
TAGAAGAGTAAATACCATCTTAGTGTTATTATCAAAATATTCTGAACTCATGAACCTCCT
CAGACTGTTGCTGGGACTCCCAGATATCAATACTCTGAGAACCACTGATCTAATGTTTCT
TTAGTCAGTTTCTATTTGTTCTCTAGTATAACCAAGCATAAAAGTAATATACTTCCGCCT
CTCTCTCCCCCAACTGACTTTAGTCAATAGTACCT

Sequence 411

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTTCGACCCACGCGTCCGC ATTTATTAAGGCTTGTATATGTTCAAGATCCAGTGAAGACTGTCTTGGG Sequence 413

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACAACTTGTGATGCTT TTGGCAGGAATTACAGAACCAATGCCATTCAAGTTGTGGAGATTATACTNGCAGGTG AACTCGTAAAGAGAAGATTCTGGAATGCCTATATCTGAAAGCTTGAGTCGACACCTN

TABLE 1 72/467

Sequence 414

Sequence 415

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTCCCAAAGTGCTGGAA TCACAGGAATGAGCCACCCACCCCAGCCAAATTGGGCACAAATTTAAAATTTGACTTTTA TTAATGATATGGTAAAGAGATCTAGCTTGGTCATGACACCCTTGTGTTATACGGTGACAG GCAAATCATTTAAAAATATCTAAACTATAATTTCCTGTAGTTCACATGAATTGGATATTC TGAAGCGGCCCCNTGGGTCGACTTTGTAACCTGCCCGGGCGGCCGNTCTAGAACTAGTGG GATCCC

Sequence 416

TATGGCGAATTGGAGCTCCCCGCGGTGGCGGGNCGAGGTNAAGCTTCGACCCACGCGTCC GATTATTCTCCCATTTAGGCTATAAATCTTTCAGTGTAGGGTGTTTCTAATGTCNTATT CTTCCAAAAAAAAAAAAAAAAAAA

Sequence 417

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGCCGCCCCGGGCAGGTGCCAAAGCCT
TAACTTAGATTGTTACTTATGTTTCTAAATCTGNGGAAGCACATTTCCTTTTNTTNTNNT
TTTCTTTTACTGTTAATATCCTTATTCTCTATTTTACCAGTGGAGAATGNTTAGTATTAA
TTTCCATTTANCTCANGATTCAAGAAATGCAAAGTGCTATTTTTATCAAATTTCTGAAAG
CCTACTGTCTTCTGNTTTGGAAGTCCCACAACAGCTCTTTAATTTCCTTAAGCCCCACTT
TCCTCATCAGCAAGTTGGTGTGGCAATGGATCATAATAGGTTGCTGGGAGGATGAAGTGA
GCGGACCGCGTGGGTCGAAGCTTGTACCTN

Sequence 419

CCGCGGTGGCGGCCGCACTTTTTTTGTATTACTTCAACTTTTAAAAATTCTAAAGAAAAC CATCATCTCAGACCAGCATTTCCGGACGCGTGGGTCGAAGCTTGACCT Sequence 420

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTGTCAAACATCT CCCTCGTCCGGATCCTTCTAACGCAGGAGTCTCAGACGCAAATGCCGGCAAGGGCCAGGC AGGTGATGTAAGATGCGTGGAGCAGATGCCAAGCCACAGGGAGTGGTGGAGACTGGGGTG AACTGGAAAGCACCT

Sequence 421

Sequence 422

GGTGGCGGCCGGGCAGGTGTCAAACATCTCCCTCGTCCGGATCCTTCTAACGCAGG AGTCTCAGACGCAAATGCCGGCAAGGGCCAGGCAGGTGATGTAAGATGCGTGGAGCAGAT

TABLE 1 73/467

GCCAAGCCACAGGAGTGGTGGAGACTGGGGTGAACTGGAAAGCACCT Sequence 423

Sequence 425

Sequence 426

CCGCGGTGGCGCCCCGGGCAGGTCAAGCTTCGACCCACCGTCCGGCAATGATGAGCA AAAACAAGTTTGGTCCCCCTGTTATAGNGCCTGGTAAAGGTTTTTGTTGTTGTTTTTGCAG GGGTGGGGAACCAGGAAATCAGATCATCACAACAATATATACTTATCTGTAACTATGGT AACTGCTACAGCAAAGGGGCGTATCATACTATTAGCATACTAAGTTTCACTTAAAGAGGT CGGA

Sequence 427

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTGTCAAACATCTCCCTC
GTCCGGATCCTTCTAACGCAGGAGTCTCAGACGCAAATGCCGGCAAGGGCCAGGNAGGTG
ATGTAAGATGCGTGGAGCAGATGCCAAGCCACAGGGAGTGGTGGAGACTGGGGTGAACTG
GAAAGCACCT

Sequence 428

Sequence 429

CCGGGCAGGTCAAGCTTCGACCCACCGTCCGGCAATGATGAGCAAAAACAAGTTTGGTCC CCCTGTTATAGAGNCTGGTAAAGGTTTTTGTTGTTGTTTTTGCAGGGGTGGGGGAACCAGG AAATCAGATCATCACAACAATATATACTTATCTGTAACTATGGTAACTGCTACAGCAAAG GGGCGTATCATACTATTAGCATACTAAGTTTCACTTAAAGAGGTCGGA Sequence 430

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Sequence 431

Sequence 437

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCACGGTACCACGTAGCAAC

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Sequence 439

Sequence 440

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCCTAAAACTTAAAGTA TAATAGTAATAATAAAAAAAAAGAGGTGCTTTTCTCCTAAGTCAACATTTTAGAGGAAAAAGA GTCAATTCAAGCAATTATCACATATGTGTAACTGAAGCACATATGTGTAACTTTTCAAGA GTGATTAGATGGTCTTTTGAAGTGATAGTCAAATATCAGGTGTTCTAGGGAG GTTGTGTAAGACCTTTTGCTTGTATTCTCCCGGACGCGTGAGTCGACTCAAGACCTGCCCG

Sequence 441

Sequence 442

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTTACAAGTCGACCCACG CGTCCGCTTCAGAATATCCAATTCATGTGAACTACAGGAAATTATAGTTTAGATATTTTT AAATGATTTGCCTGTCACCGTATAACACAAGGGTGTCATGACCAAGCTAGATCTCTTTCA TATCATTAATAAAAGTCAAATTTTAAATTTGTGCCCAATTTGGCTGGGTGTGGTGGCTCA TTCCTGTGATTCCAGCACTTTGGGAGACCT

Sequence 443

CGCCCGGGCAGGTACACAAACCAGATGTATGCAATGATGCCAAAAGTCATCTCAAAATTC
CAAGCTGACCTAGTGCAACACATTTACACTTGGATAAACTATCACCTTGAAGATTTACTT
TGTATACTTCAAAAGATCTGGTCATGAAATTTTTAGCTAATACATAAAGTGCCGAATTGA
AATCCAGAATACAATAGCTATGAAGGGCCGNTAGAGTGCAGATAACCAACCCATTCTACC
TAACTCAGGTTGAGATTGCTTTANAACCTATCATTGGCTTTAAAATGGTCCACAAAAAAA
CACCTCATGGTCACACTTAAA

Sequence 444

ACNGNCAGGTACCAAGATTAAGGACAGAGTTCCCTCCATTGGTCATTGATTTGNAAACCA AAATGTATCTGTGACAGGTATTAATCCGGACGCGTGGTCGAAGACGAAAGGACACGAGAA ATANGGACCTANNCCGCTCTANAACTAGGNATCCCCNNNNCTGCAGGAATTCGATATCA

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Sequence 445

CCGCGGTGGCGCCCGCCCGGGCAGGTGCCAAAGCCTTAACTTAGATTGTTACTTATGTT
TCTAAATCTGTGGAAGCACATTTCCTTTTCTTCTTTTTCTTTTACTGTTAATATCCTT
ATTCTCTATTTTACCAGTGGAGAATGTTTAGTATAATTTCCATTTANCTCAAGATTCAAG
AAATGCAAAGTGCTATTTTTATCAAATTTCTGAAAGCCTACTGTCTTCTGCTTTGGAAGT
CCCACAACAGCTCTTTAATTTTCTTAAGCCCCACTTTCCTCATCANCAAGTNGGTGTGGC
AATGGATCATAATAGGTTGC

Sequence 446

CGGGCAGGTACCCTTATTTTCCCTGATACAGCACAACTCTGCCTATTCTAATCATGACCT AGACACATTCAATGAACTACAAGTTCTCCTTTACACGGACGCGTGGGTCGACTCCGGACG CGTGGGTCGAAGACCTCGGCCGCCT

Sequence 447

Sequence 448

GCGGCCGCCGGCAGGTTACAAGTCGACCCACGCGTCCGCTTCAGAATATCCAATTCATG
TGAACTACAGGAAATTATAGTTTAGATATTTTTAAATGATTTGCCTGTCACCGTATAACA
CAAGGGTGTCATGACCAAGCTAGATCTCTTTCATATCATTAATAAAAGTCAAATTTTAAA
TTTGTGCCCAATTTGGCTGGGTGTGGTGGCTCATTCCTGTGATTCCAGCACTTTGGGAGA
CCT

Sequence 449

CGCGGTGGCCGACCAGTGCAAATATCTACCCAGTTAGAAGAGTAAATACCATCTTA GTGTTATTATCAAAATATTCTGAACTCATGAACCTCCTCAGACTGTTGCTGGGACTCCCA GATATCAATACTCTGAGAACCACTGATCTAATGTCTTTAGTCAGTTTCTATTTGTTCTCT AGTATAACCAAGCATAAAAGTAATATACTTCCGCCTCTCTCCCCCCAACTGACTTTAGT CAATAGTACCTCGGCCG

Sequence 450

Sequence 451

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAGCTTCGACCCACGCG

TABLE 1 77/467

CCGCGGTGGCGGCCCGGCCGGCAGGTTTTATATTTTTTTCCTCTTTAAAAAATAATTTG GTTTTGAATATTAAATTTACATATTTCTAAGTTAAATCAACATTCGTAGAGGAATTATCA AAAAAAACTAGTAAGTCTGAAAAAAAAACCATATTTTATATTCTGAGGTCCCGGACGCGT GGGTCGAAGCTTGACCT

Sequence 453

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCGGCAGGTACCCAACACAAACTA
TTCAATAAAGTAATCTGCTTTAAAAATAAAACACACTGAAAGGCCGAGGCAGGTGGATCA
CCTGACATCATTAGTTCAAGACCAGTGTGGCCAAACTGGTGAAAATTAGTCTCGACTAAA
AATCAACATTAGCTGGGCGTGGTGGCAGGCGCCTCTAATTCCAGCTACTCAGGAGGATGA
GGCAGGAGAATCACTTGAAGCAAGGAGGTGGAAGTTGCAGTGAGCTGAGATCGTGCCATT
GCACTGCAGCCTGGGCAACAGAGTGAGACTCCGTCTCAAAAACACCACCACCAACAAAAT
AAACACAACAGAATTATTCTGCAAATACAGATATTGGAGTAGCTGAGTTCCATCTCAAAT
TTGACTATGCAGGTTGACAGGTGATCTTGGCAAACTACTTATCCTTTCTGAAGTTCAACT
TTTTCACCAAATGGTATTGGGATACAACACTTGCTCTTGCCTATCTCACATGAATTATCC
ATTTTGGACAACTTGGTAAACTATA

Sequence 454

Sequence 456

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CATCTCCCATTTATTTTTCATTTGAAATAAAACTTTTGAATTTTATCTTCTACCTAAATA
ACATATTTTGTTTTATGTTTCAAGATGAAGCTCACACTGAGTTGGAAAAAAGGAAAAAGC
AAAGGATCAAAGCTGGGGGAAAATACTGGACCATGTGCTTCACCTCATGGTGCCAAATAA
AGAGAAAATGGGGAGAAGATAGGGACAGATAAAGATCTATTTGCTCGGATTGNGCTCTCA
TCCTTGGCAACATGTTGACAATGCCCTGGAAATA

Sequence 458

Sequence 460

CCGCGGTGGCGGCCCGGGCAGGTCTTCGACCCACGCGTCCGTGATTGCCTATTGTT
TGTTGATTGACTGATTTATGCCTCTAAGAGGAACTATCTTTTGATAATAATAAGAT
GTCCTAATACAAAACTGATAGAGTTCAGAAATAATAAGAATCTCCTGGCCAGGCGTGGTG
GCTCACGCCTTTAATCCCAGCACTTTGGAAGGCTGAGGTGGGCGGATCACGAGATCAGGA
GATTGAGACCATCCTGGCTAGCATGGTGAAACCCTGTCTCTACTAAAAATACAAAAAAA
TTAGCCCGGGTGTGATGGCGACCT

Sequence 461

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Sequence 463

Sequence 464

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ACTATNGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTGTCGACTCAAGCTTTCAG ATATAGGGCATTCCAGAATCTTCTCTTTACGAGTTCACCTGCTAGTATAATCTCCACAAC TTGAATGGCATTGGTTGTTCTGTAATTCCTGCCAAAAGCATCACAAGTTGTACCTGCCCG

Sequence 465

Sequence 466

CCGCGGTGGCGCCCCGGNCAGGTTACAAGCTTCGACCCACGCGTCCGGGAAATTTTA
ATTAAAAATAGGTGAACATTTTAAATGACCTAATACATATTTAGTCCACATTGAAACTTT
GGCATTTTGTCATTGCCATTAAAATTTTGATGGCATTAAAATTTTGATGCCATTAAAATTT
TGAT

Sequence 467

Sequence 468

Sequence 469

GACCTCTTTAAGTGAAACTTAGTATGCTAATAGTATGATACGCCCTTTTGCTGTAGCAGT
TACCATAGTTACAGATAAGTATATTGTTGTGATGATCTGATTTCCTGGTTCCCCCACC
CCTGCAAAACAACAACAAAAACCTTTACCAGGCTCTATAACAGGGGGACCAAACTTGTTT
TTGCTCATTGCCGGACGGTGGGTCGAAGCTTGACCTGCCCG

GCTCCCGCGGTGGCGGCCGCCCGGGCANGGTTACAAGCTTCGACCCACGCGTCCGGGAA ATTTTAATTAAAAATAGGTGAACATTTTAAATGACCTAATACATATTTAGTCCACATTGA AACTTTGGCATTTTGTCATTGCCATTAAAATTTTGATGGCATTAAAATTTTGATGATGCCATTA AAATTTTGAT

Sequence 471

GCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTCAAGCTTCGACCCACGCGT CCGTGATAACTTCTCCTAAGTGCCAGGCATTGTATTACATGCTGGGAGCACAAAGATGAA TAATAACAATAGGTTCACAGAAAAGATGAATTGATTGAGAGAAAAAGAACCCTCCAGGAG CCCTCAGCGTAGTAGGGGGTTGGTGTTGGAGGGTNGGAGGAATGGANAAAGGCCCTGAAA TGCAGGCAGAGAAATGATGAAACAATTCAGGGGCTGTGGTGAGGTTAAATGAATATCTT Sequence 472

TABLE 1 80/467

CGAAAAAAGAAAGAAAAAAAAACTTTCTCTTTGCCANTTCTTCTTCTTTNTT Sequence 473

Sequence 474

CCGCGGTGGCGCCCCGGGCAGGTACACAAACCAGATGTATGCAATGATGCCAAAAGT CATCTCAAAATTCCAAGCTGACCTAGTGCAACACATTTACACTTGGATAAACTATCACCT TGAAGATTTACTTTGTATACTTCAAAAGATCTGGTCATGAAATTTTTAGCTAATACATAA AGTGCCGAATTGAAATCCAGAATACAATAGCTATGAAGGGCCGCTAGAGTGCAGATAACC AACCCATTCTACCTAACTCAGGTTGAGATTGCTTTAGAACCTATCATTGGCTTTAAAATG GTCCACAAAAAAAACACCTCATGGTCACACTTAAAATAGTTTGCATCCCACACTACAGGCT TCTCTGGAGGATTTAATACTTTGGAAGTAGCATCATAAG

Sequence 475
CTNCTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGACCNGTGCAAATATCTACCCA
GTTAGAAGAGTAAATACCATCTTAGTGTTATTATCAAAATATTCTGAACTCATGAACCTC
CTCAGACTGTTGCTGGGACTCCCAGATATCAATACTCTGAGAACCACTGATCTAATGTTT
CTTTAGTCAGTTTCTATTTGTTCTCTAGTATAACCAAGCATAAAAGTAATATACTTCCGC
CTCTCTCTCCCCCAACTGACTTTAGTCAATAGTACCT

Sequence 476

Sequence 477

Sequence 478

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTTATACTAGAA
GATGCTCCAAGGTTTCAGAAAGGAATTACTTTCAATTTGCACAATTTAGAACAAAT
ATCTGGCTTTTCCCTAAGCTTAATGATTTTCCATTTCACACAACTAAAATATAATAGCAT
TATTTTATAATCAAGTTTAACTGATGGTCTATGATAGTAGTAGGACGATTTAGTATTTTGACA
AAAATCTTATGAGACATGAAGTCATTCAATTTGCCGGACGCGTGGGTCGACTCAAGCTAG
ACCTN

Sequence 479

TABLE 1 81/467

AGGGCAGAGGTATGTGTGCGAGCTCAGATACCTTAAATTCATATGCCTTTAATACAATCC
AGGCAGATTTCTAAATGAGGGATGCTTCCCCACAAATGGAGAGTGAAAGTGGGCCAGCCT
AAAAGGACCTCCATAGCACTGTGCATGGCCAGCTGTTTGTGGCTGTACC
Sequence 481

GACCTCTTTAAGTGAAACTTAGTATGCTAATAGTATGATACGCCCTTTTGCTGTAGCAGT
TACCATAGTTACAGATAAGTATATTGTTGTGATGATCTGATTTCCTGGTTCCCCCACC
CCTGCAAAACAACAACAAAAACCTTTACCAGGCTCTATAACAGGGGGACCAAACTTGTTT
TTGCTCATCATTGCCGGACGGTGGGTCGAAGCTTGACCTGCCCG
Sequence 482

CCGCGGTGGCGCCGCACTTTTTTTTTTTTTTTTTTTACCTGAAAATGCTTATTCTAGCTT CACATTTGATTGTTTGGCTAAGAAGAAAATTATTTATTAGACTTAATTTTCCTCACGAGT TTAAAGATTGCTTCAGATCTTAAACTTCTAATGAGGAAAGCTGAGAAGTCCAATGCCATT CTGATTCTTGCAACTTACAAGTAGTCTTTTTTTTGTCTAGACGCTTTCAGGACCTTCTTTT TTCCTCAGTCAGTGTATCCAAACCTTCACAGTGATATCTTTTGGGTACCT Sequence 486

Sequence 487

Sequence 485

CCGGGCAGGTACAAATCAAGTCATTAACATTTTCAATGTCAAAAATACAGCACGCTGTTA AGAGTTCTGTCAGTGCTCATTATCCCACTAGATCCCACAAAGGGCAAACTCAAAAGATGA AACAAAGGCAACGCCATCAATAACCACCATATTCCACAGGCTTTCTCCCCTAGGACGTAC

TABLE 1 82/467

CTN

Sequence 489

Sequence 490

Sequence 491

CCGGGCAGGTACAGCCTCACATACACAGATGCAGGTGAAGTCACCAAAGCTGATCTCTCA TTCGTTCTGGGGACAGTTAGCAGCGTAGTGGTCCCACTGCAGCAAAAGTTTGAAATTCAT TTTCTTCAGGAAAATACCCAGCCAGTCCCTCTCAGTGGAAACCCTGGTTATGTCGTGGGG CTCCCATTAGCTGCTGGATTCCAGCCTCATAAGGGTGGAGCTCTCCCGTGTCAGCTCGTA GCACAGAAGGTGAAGAGCCTGCTGTGGGGCCAGTGCTTCCCAGATTACGTGGCCCCTTTT GGAAATTCCCAGGCCCAGGGACATGCTGGACTGGGTGCCCATCCACTTNATCACCCAGTC ATTCAACAGGGA

Sequence 492

CCGCGGTGGCGGCCGAGGTACTATTGACTAAAGTCAGNTGGGGGAGAGAGAGGCGGAAGT ATATTACTTTTATGCTTGGTTATACTAGAGAACAAATAGAAACTGACTAAAGAAACATTA NATCAGTGGNTCTCAGAGTATTGATATCTGGGAGTCCCAGCAACAGTCTGAGGAGGTTCA TGAGTTCAGAATATTTTGATAATAACACTAANATGGTATTTACTCTTCTAACTGGGTAGA TATTTGCACTGGT

Seguence 493

ACTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGTTAAAGGAATAATCTGCAGA ACATCTTGATTTACAAGGGACAAAATGATGCAAATTATATGCTGTCCAACCTACTGGTGA ACTGGATCAGAATGGTCCAAGGACTGTTAAACAGAGGAAGTATTTACATTTTGAAAAACTT GCGGACGCGTGGGTCGAAGCTTGTACACCT

Sequence 494

CCGCGGTGGCGGCCGTTAAAGGAATAATCTGCAGAACATCTTGATTTACAAGGGACAAAA TGATGCAAATTATATGCTGTCCAACCTACTGGTGAACTGGATCAGAATGGTCCAAGGACT GTTAAACAGAGGAAGTATTTACATTTTGAAAACTTGCGGACGCGTGGGTCGAAGCTTGTA CACCT

Sequence 495

Sequence 496

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Sequence 497

CTACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCCCCAGGTC
AGCACTTTGAACACTTGAACATCTATGAAATCACATAGTAAAGTGATAGGAGATGGGGCT
AAGCTTTTAATGGCCTTTAGACATAGCATTAGACATAACCTAAGCTGAAAGGCTTTGGGA
AGTTGTTGTGTTAAATCCCCAACACACTCTCGTGTTTTCTTAGGACTTGCCTNTTATTTA
AAAAAAAAAAAAAAAAAAAGTTGCGGCCCGCTCTAGAACTAGTTGGATCCCCCGGGCTTGCAG
GN

Sequence 498

Sequence 500

Sequence 501

CCGCGGTGGCGCCCCGGGCAGGTCAGGAGTGTCCCAAAGATTTCCCAAGTCCAGCCC AGAGAAGCTGAAAGCCTTTCCCCCAGGTGTGGGGCTGAGTTAGATGTGGGTCATAAAGGA TGTGGCCTCGAGGCTGGGAGGCAGCTGGGCAAAGTGGGAAGCCTCCCTACTCCTGAGACA GTGATGGCTCAAATCCAGGCCAACCTGGAACATGATCCTCAACTTCTCTAAGTTCACCTT TCCCAGGTGTGAAATGGGTTGTTCTGGGAATTGAGTGAGCTAATGATACACTCCCTGGCA CACAGCGAGCCTNAAAACGCTTGTGTCCCCTCCCTACCTCACAGCCCATTTTAGAAGTTT GCTGTCACTTA

Sequence 502

Sequence 503

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Sequence 504

CTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAGCTTCGACCCACGCGTC
CGAAATTCTTGGTTAAGGATTATTATAAAATAGAATGGTATTTCAGTAAATCCCTGAGGC
TTAGGAGTCCAGGTACAATGTTGGTTCTCAATTAAAATATAAATCATGTCTAGGGACACT
TAGGAACACAGAACATATATTTAGAGCTAGAAAATATACAGCTTCAGACCAGGCAAAGTG
CTGGGATTACAGGCGTGAGCCACCACGCTCGTCCTCACATGGGGTTTTATTATTAGGATG
GTAAGAGTATTATAAGGGATTNGGTACAAGGCATAATGAGTCCTTTTTGCTTTTTAGGCTT
TTGACTTNTGGTTTTAAGACTTTTNTTTAGCTTTTTTGTTNGTTAGACANCCATTTGGGCA
AGGCTTNGGTTTTTTAATAAAGTTTGCTTGGGGATNAAACNTGACCTTAATGGAAATTGTC
CCCTNCCCCCAAAA

Sequence 505

CCGCGGTGGCGGCCGCCCGGGCAGGTACTACTGATACAAATAGCATGGATGAAACTCAAA ATCATTATTCTAAGAGCCAGATACTATAGCCTGTATTTTATGATTCACTTTCAATGAAAT TCTACAATAGACAGAACTATCTATCAACAGAAAGCAGATCAGTGGTTTTCTGCAGCCAGA GGTATGAAAGGTTTGAAACATGTGGCACCAGTAGGACATATGGAAACTTTTTTGGTGTGA TGGAAGTATTTTTTTATCTTGATTGTGTGTGTTTTTTATCAGTGGTATACATTTGACC

Sequence 506

GGGGCGCCCCGTTCAGGTACACGTNTTTNCCAACCAATTTTATANGNATATATAT TCTACTTCCAACACCCNTNTTCATCCTGGTNCAATCAAAGCCTGGTTNTGGCCAACAANA AACTCGTCAGGAGATCGAAGGNTGTAGATGTCTGCACGTGGCTTCCTTGGAGGTCCAGNG GNGACTCCCTCTCCAAAATCCATTCTGTACCCGCTGGCTGCTCTAACGGGCAGGACAAC AGCGTATGAAGCCTGACTGCAACTAGGAGAAGTACCACACTCCCGGACGCGTGGGTCGAA GCTTGTACACCT

Sequence 507

GGCCGAGGNCAAGCTTTTACCCACGCGTTTGAANCCATCTGTTTGGNACCCNGAAAGGGG
GCAGGAAAGGCTGGGGTCCCAGNCCACCCTAAGGGNATCTGAGTGGCCCAGGGCTNCAAG
NNNCCCACCTGNCCAATGGGACCCTTTCTGNCCTCACCCTACAAGGGGCACAAAGGGAA
GACACCAAACCTGGCAGGAACTTTTCACGCAATCAAGGAAAGGCANTCCTGGCAG
AGGGAACAGCANGCCAAGCGGGAGAAGGCTCAAAGTAAGGAGGGTAAG
Sequence 508

CCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTCCGCTTTTCAATTTATTGTAT
AGTTTTTGATAATGTTAATGTCTGAGATCTTTATGGGTGAGTCTGCTGTCATTTCTGCTA
TTTCTCGTAGTGATTTGCTTGTATGGTTTATGATTTTTTAAAAACTGAATGTGTATTAGA
ATTGTGTCTGGTAATTCTTTAGGGACCCATTGTAGATGTATTTCTTCAAAGAGCATTTGT
GGTTATTATATTTTGGGTGCTTGGGGCACTGCCAGTACCTGCCCG

Sequence 509

CCGCGGTGGCGGCCGAGGTATTGAACCAGGTCAAAACATTGTTGAATATCAAACCCAATC TATTTAATCTGTAAGAAACAAGGACCCTGAGAAAGATTCTGACCAAGGGTATGTGATCGG AAACTTGACAGATAAATGTAGTATACTTGTAAAGCCATACTGTGAAAAACTTGGGGATTA TTTGAACACAAATTATCACCTGGAAAAAGACAGAAAACAAGGCAGAAGACTGTGCAAAGA GGTTGGAATATTCAAAACTTCAGATTAGAAG

Sequence 510

CCGCGGTGGCGGCCGAGGTACCCAANNGATATCACTGTGAAGGTTTGGATACACTGACTG AGGAAAAAAGAAGGTCCTGAAAGCGTCTAGACAAAAAAAGACTACTTGTAAGTTGCAAGA ATCAGAATGGCATTGGACTTCTCAGCTTTCCTCATTAGAAGTTTAAGATCTGAAGCAATC

TABLE 1 85/467

CCGCGGTGGCGGCCGCCACGCTTGGCCGCCCGGGCAGGTCAAGCTTCGACCCACGCG TCCGAAATTAATGAAATGTTTTACATTCTTTTAAAAACCTTTGAAATATGGTGTGTATTT TATGCTTTAGCAAATCTCAGTTTGGACCATTTCAGGTGGTCAGCAATTACACATGGCTAG AACTAAGAGCAATCAGTTTTNTTCCACAGTTTTTCTAAAATTTTCTTGTCAAAAATCTTG ATGGTATGAATTACTCTTTTAAAAAGTGCACTTNACCAGCAACAGAAAANAACCCTGGAG GGGTATGGGTTTTAAAGCTGGTACCTNGGCCCGNTCTAGAACTAGGTG Sequence 512

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTCCCAAAGTGCTGGAATCA CAGGAATGAGCCACCACCCAGCCAAATTGGGCACAAATTTAAAATTTGACTTTTATTA ATGATATGGTAAAGAGATCTAGCTTGGTCATGACACCCTTGTGTTATACGGTGACAGGCA AATCATTTAAAAATATCTAAACTATAATTTCCTGTAGTTCACATGAATTGGATATTCTGA AGCGGACGCGTGGGTCGACTTGTAACCTGCCCGGGCGGCN

Sequence 514

Sequence 513

Sequence 516

Sequence 517

TCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTCCGGAGAAATACCATTTGCACA
GTCAATCACTTCTGACCAAGCTTATCAGAAAAAGGAGAAAAGAATGTCTCCCCACTAAAT
GTTCTAGGGNGGGNGAGGAAANCTAGGGTGGNTATCTAAATCAACAAATATTCTAGATAT
TCCAATATCTAAATTATTGTTGGAAATACTCNTCCTGAAGNGNTCATTTGAACNCTAAAG
CAGGAGNACAGCNTTTGTTGTATCAANATGGGCAGGGGTTTTTAAAGGGTNTCCATTTTT
TNTTANTTTCCNCATTATTAAATTCCNTTNTAAATNNTTTTTAGGACCAAAAATTTTTCC
CNTTTCTTNGAGGTNTTTAAAGGGGGGATTTAANAAAAATGGGNNANNTGGGGGGTTT

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Sequence 518

Sequence 519

ATTGGAGCTCCCGCGGTGGCGGCCGAGGTACAATGCTTCGACCCACGCGTCCGCTCACT
TCATCCTCCCAGCAACCTATTATGATCCATTGCCACACCCAACTTGCTGATGAGGAAAGTG
GGGCTTAAGGAAATTAAAGAGCTGTTGTGGGACTTCCAAAGCAGAAGACAGTAGGCTTTC
AGAAATTTGATAAAAATAGCACTTTGCATTTNTTGAATCTTGAGCTAAATGGAAATTAAT
ACTAAACATTCTNCACTGGTAAAATAGAGAATAAGGATATTAACAGTAAAAGAAAAGAAA
AAGAAAAGGAAATGTGCTTCCACAGATTTAGAAACATAAGTAACAATCTAAGGTTAAGGC
TTTTGGCACCTGCCCGGGCGGCCCGCTCTAGAACTAGTGGGAT

CACTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTCTTCGACC CACGCGTCCGAGCTATGGACCTAAGGCAGCGAGTGGATTCATTAGTCCTCTTTCAGCTGA ATGCATGCTACAGTATAAGAAAAAAGCTGCTGCCTATATGAAGTCTTTGAGAAAAGGTTTG TTAGCTGCTGTTAATATTTAAATCAGAGGAAACATCAGGAGTCATTCTAGAGAATGGCAA GAGTTTTTCTGCAGTTTATATTGTTGACTTTTTATACGATATTGGGGTACCTCGGCCGCT CTAGAACTAGT

Sequence 521

Sequence 520

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGCCGCCGAGGTTCGACCCACGCGTCCGC
TAGGAACTATGTTAAAAAAAATTCAAGAAAGAATTTAAGGGAGATTACAGTGTTACTGTG
ACACCAGGAAAACTTAGAACTTTGTGTGAAATAAGACTGGCCAGCATTAGAGGTGGGTTG
GCCATCAGAAGGAAGCCTGGACAGGTCCCTTGTTTCAAAGGTATGACACAAGGTAACCCG
TAAGCCAAGGCACCCAGACCAGTTTCCATACATAGAACCTGCCCG
Sequence 522

CTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTCCCAGAATA
ACTAAATAAATAAAAGGCTAAAGAAAACTGGAACAGTACTGCGTCTCCATCTGAGACGCA
NTCTTCTACTTCCAGCATCGNAGAGAAGGGCTAGGGACAATTTTTTTTTCAAAAAGATTTAT
ATACAGGCTTGAATCCAGAAATTAAGGNTAAAAGCATAAATATTGATAATTTCAACTAAA
TTCAGAATGGNTTCAGAAAGATATGATACAACAATTTAGAATAAAACAAAGCAGAAGAGC
ATNATATTTTGCGGACGCGTGGGTCGAAGACCT

Sequence 524

CCGCGGTGGCGGCCGAGGTGTACAAGCTTCGACCCACGCGTCCGCTTAAAAGATTTTTTT
TTTATGTAAACTGTTGAATATTTGAAATAGTCCACTTCACCTTAATGGGTCTTGTCTATC
TTCATTAGTCTTCAAAGAAAAACCATTTGCTACCAAAGTAAATCAGTATTTTGAATGTGC
TTCTCTTGTTTTTTGTTTATTAGCTAGTTCCTGTAAGCATTTCCACCAGAACTTGAGGCA
AATCGTAAGGAAGCTGTTTCTTTTAAAACACAAACCACCACCAAAAATTTAAATGTACCT
GCCCG

Sequence 525

CTACTTAGGGCGAATTGGAGCTCCCGCGGTGGCGGCCGAGGTTTCAAGACCCGCCTGGC

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Sequence 526

Sequence 527

Sequence 528

Sequence 529

Sequence 530

Sequence 531

CTACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTTAATCCCGTCTTAC

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Sequence 532

CGCTACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAATAAGCCCACCC CACTAGGAACTATGTTAAAAAAAAATTCAAGAAAGAATTTAAGGGAGATTACAGTGTTAC TGTGACACCAGGAAAACTTAGAACTTTGTGTGAAATAGACTGGCCAGCATTAGAGGTGGG TTGGCCATCAGAAGGAAGCCTGGACAGGTCCCTTGTTTCAAAGGTATGACACAAGGTAAC CCGTAAGCCAAGGCACCCAGACCAGTTTCCATACATAGAAAGTTACAGCTGCTTTTATAC CCCCTTGCCCCGCCAACGTAGT

Sequence 533

Sequence 534

CCGCGGTGGCGGCCCGGGCAGGTGTCCCCATGAGGGCCACGGCCCAGGCAGAACCCA TCCCATTTTATCCTTAAACTCAGAAGGAAATTTGTCTAAATATTAAAGGATTAATATGGG AATAAAAAATGAACCTTAAA

Sequence 536

GAANTGGAGCTCCCCGCGGTGGCGGCCGAGGTCCAGTAGATTTGGAGAGTAATACAAATC
CTTTCTTTCTGGTTAGAACACACTGCCAAAAGCCACCTCTTTCATCTAAGGAAAAGATTA
AAAATGCATGTTGATATCTCCTAACTATCACACAACTTCCACTATTACAATGAAAAATCT
GGTCCCCTTTCATTGCCTTTGAAAACCNTTTTGCCGAGGTGGNTTTCAAAAAAACNCGNG
ANTTTTNAAAAANTTGGNTTTGGTTTTACCNGGGGAAAGGGGACNTTTNNCNNTTTTTT
TTTTTTTTTTTTTTTTNAAANGGNGATTNGGTTNNGGTTNTCCTGGGGCCAAAATNCC
NTTTTGNGGAACCTTTTTTGGGGTCCNAAAANNNACAAAANAAAGGGNTTGGGACNATNT
TTTTGNATNCNCNCNAAAAAAAATTTTTTTTTTT

Sequence 537

ACTTAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGAGGTTCGACCCACGCGTCCGCTA GGAACTATGTTAAAAAAAATTCAAGAAAGAATTTAAGGGAGATTACAGTGTTACTGTGAC ACCAGGAAAACTTAGAACTTTGTGTGAAATAGACTGGCCAGCATTAGAGGTGGGTTGGCC ATCAGAAGGAAGCCTGGACAGGTCCCTTGTTTCAAAGGTATGACACAAAGGTAACCCGTAA GCCAAGGCACCCAGACCAGTTTCCATACATAGAACCTGCCCG Sequence 538

TABLE 1 89/467

AGGCCCTGA

Sequence 539

AATTGGAGCTCCCGCGGTGGCGGCCGAGGTGACAAGCTTCGACCCACGCGTCCGCAAGT TTTCAAAATGTAAATACTTCCTCTGTTTAACAGTCCTTGGACCATTCTGATCCAGTTCAC CAGTAGGTTGGACAGCATATAATTTGCATCATTTTGTCCCTTGTAAATCAAGATGTTCTG CAGATTATTCCTTTAA

Sequence 540

TACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTCCCATTTCCCTGAAAC AAGCAGCCAGCAACTATCTCAGAAATGTGTCATTTTACTGGTTATAATTCTTAAAAAGC TTGTTTTCCTAAGATATGAAATGCCTGCCAGTATACAAACTGTTGTAACTACTTCCCTTT TTGCTTTTAGCGGGGAAAAAATAGCTTAATGACAGCATAGAATCATGTAGTAAATAAT TCATTTTTTGAAAGGTTCAGCTATATCCTCTTCCATTTGTTTATTTTAAATGATCTAATT GCAAACATGTCATCACTCCCTT

Sequence 541

ACTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACATTGGA TTGTTAAAAGAGGAGTCTAGAAAAATTAATCCTGAACCCTAAAGAATAAATCTTAAGTGG TGGATACATGGGTTGAATAGTGTGCTCCAAAATTCACATCCACTTGAAACTTCAGAGAGT GGCCATATTTGTAAATAAGGTATTTGCGGGTGTAATCAGTTAAGGATCTCAAGATAAATT CATCCTGAATTATAAGTTGTCCTTAAATCCAATTACTGGTATCCTTACAAGAAGGTGAGA GGAGACAGAATAGAGCCATCTGAAAAGGGTCAGAAA Sequence 542

CTACTATAGGGCGATTGGANCCTCCCCGCGGTGGCGGCCGAGGTACTTCCTGGAAATCAA
TTAACTGAGTCTTTTGAAACCCCTAGAGAAGATAGGAGAAAATTGGTTCAGANCGAGCAT
TTAAATTAAGTCAGCAAAGTCAGAATTTAAAATTGGGCAATTCCTTGTCTACATTTTCTT
TACACTCAA

Sequence 544

CTNACTATAGGGCGANTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTGCCAAAGCC
TTAACTTAGATCGTTACTNATGTTTCTAAATCANGTGGAAGCACATTTCCTTTTCTT
CTTTTCTTTTACTGNNAATATCCTNATTCTNTATTTTACCAGTGGNGAATGTTTAGAATT
AATTTCCATTTAGCTCAAGATTCAAGAAATGCAAAGTGCTATTTTTATCAAATTTCTGAA
AGCCTACTGTCTTCTGCTTTGGAAGTCCCACAACAGCTCTTTAATTTCCTTAAGCC
Sequence 545

Sequence 546

Sequence 547

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Sequence 548

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGNAGGGTCGCGGTGGGTCGA CTNANGCTAGAGAATTGTAATACGACTACTATAGGGATCTAGATCACGAGC Sequence 549

Sequence 550

CTATAGGGCGAATNGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCANGTGCTTCGCCCCAC
GCGTCCGNAATAATTGGAAANGGCCTATAGATTAAAAAGCTGAGAAAGTATATGGTAGGG
AGCACACTCCCCACAAGTATGAACTCTGNGATTACGACATCTCATAAATNCATGAGCACT
CATGTTGGCTTGCTTTGTAGCTATGAACTTACCCTGTATTATTGAAACGTCAGCATAATG
ACTGGAAGGAGAAATTGGTCCATTTTAGAAGCATTACTATTATGCTATCTGTCCATTTAAA
TTAATAATTGCATTAAATTCATTTTAGAAGGNGCTATTACATTNGTAGTAAGAAAGTAAA
ATAGGAGAGTTTACCTGAAGAAAAAAAACTTTTNACTTTTCTGGGAAAAAAA
Sequence 552

CTACTTAGGGCGAATTGGAGCTCCCCGCGGNGGCGGCCGCCCGGGCAGGTACCAAGTGAA
TTTAAATAATTGGTGTGGATTGGCCAGTAGCTAAGAAGTGGGCTTTTAAAGAGTNTTGAA
NATNGAANGGGTTTTTNTTTCTTTTTTAAAAAAAGAAAACAAACTATTGATTGTCTATAA
TGAAAAGCTAGGNNTTGCCCTNTTCATGTNTACTCTCCTTCCAAATAGTTATATCCAAAA
CTGTTTTTCCCTCCCCTACCTTGTCCCCCCTATTAAAATANAAACNGGGATTGATTAA
TGTCCCGCTCCTGAATACATGTAAAATTTGTACCTCGGCCGNTCTAAAACTAG
Sequence 553

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTC
CGCTTGTCAATAAAAAACAAACAATTGCTAAATAAAACAACCTGAGAAAATCTCCAGAGA
ACTATACTGAGTGAAGGAAGAAAAATCCCCAAAGATTACACACTGTATGTCATTTATATA
ACATTCTTGAAATGACACAATCACAGAAATAGAGAATACTGGTCACTANTGCATTAAGGA
AGGTGTGGAAGGATGTAGTGATGGGAGGAAATGTGTATGGCTGTAACAGGGCAACAGAGG
CNTCATTGTGATGATGGAAGTGTTCTGTNTCTTGGGTTTTTTGAATGTCA
Sequence 554

CACTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGTTAAAGGAATAATCTGCAG AACATCTTGATTTACAAGGGACAAAATGATGCAAATTATATGCTGNCCAACCTACTGGTG AACTGGATCAGAATGGTCCAAGGACTGTTAAACAGAGGAAGTNTTTACATTTTGAAAAC Sequence 555

TABLE 1 91/467

CTACTTAGGGCGAATTGNANCTCCCCGCGGGGGCGGCCGCTAAAGGAATAATCTGCAGAA CATCTTGATTTACAAGGGACAAAATGATGCAAATTATATGCTGTCCAACCTACTGGTGAA CTGGATCAGAATGGTCCAAGGACTGTTAAACAGAGGAAGTNTTTACATTTTGAAAACTTG CGGACGCGTGGGTCGAAGCTTGTACACCTT

Sequence 556

Sequence 557

Sequence 558

ACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTTCGACCCACGCGTCCGC
ATTTATTAAGGCTTGTATATGTTCAAGATCCAGTGAAGACTGTCTTGGGCGTGTATAATT
GATCTTAACCACAAGGCTGAGAAGTTATGTGCAGGGCTTATGATGCTACTTCCAAAGTAT
TAAATCCTCCAGAGAAGCCTGTAGTGTGGGATGCAAACTATTTTAAGTGTGACCATGAGG
TGTTTTTTTGTGGACCATTTTAAANCCAATGATAGGTTCTAAAGCAATCTCAACCTGAGT
TAGG

Sequence 559

Sequence 560

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTGTACAAGCTTCGACCCACG CGTCCGCAAGTTTTCAAAATGTAAATACTTCCTCTGTTTAACAGTCCTTGGACCATTCTG ATCCAGTTCACCAGTAGGTTGGACAGCATATAATTTGCATCATTTTGTCCCTTGTAAATC AAGATGTTCTGCAGATTATTCCTTTAA

Sequence 561

Sequence 562

TTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCCCGGGCAGGTGCCAAAGCCTTAACT
TAGATTGTTACTTATGTTTCTAAATCTGNGGAAGCACATTTCCTTTTTCTTCTTTTTTC
TTTACTGNTAATATCCTTATTTTACCAGTGGAGAATGTTTAGTATTAATTTCC
ATTTAGCTCAAGATTCAAGAATGCAAAGTGCTATTTTTATCAAATTTCTGAAAGCCTAC

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TGTCTTCTGCTTTGGAAGTCCCACAACAGCTCTTTAATTTCCTTAAGCCCCACTTTCCTC
ATCAGCAAGTTGGTGTGGCAATGGATCATAATAGGTTGCTGGGAGGATGAAGTGAGCGGA
CGCGTGGGTCGAAGCTTGTACCT

Sequence 563

CTACTATAGGGCGAATNGGAGCTCCCCGCGGTGGCGGCCGAGGTACCCAGTAATCACATA
AATTCTGCAATCATCTTTTTTTTATTTGTTGAAGTTGT
TGTTGTTATTNCAGTCTTTTTCTTATTGGGTTGACCAGACTTGGTAAAATCTGTAAGAAA
GTTCCATAAT

Sequence 564

CTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTCC
GTGCAAATTTGACTTTGTAAATGGCCCTTGGGCTCTGGGAGGAAAGCAACTGTTGGGCCA
TGTGGTTGTATCTTTAGTTTTGTAAAGAATTGCCAAACTGTTTTATAATGTGGGTATATC
TTTCCACACTTCCAGCACAATGTATGAGTGATCCAGTTTCTTAGCACCATAGTCAGAATT
TACTGTTGCTACTATTTTTTAGCTATCCTGATAGATGTGTAGTGATATTTTATTCTGGTT
TTGAAGCAGTGTCATTGTCTGGGGTAAATCCTTGAGGTTTGTTGTCTCAGTCAAGGGGAA
TCAAGGGACATGGACACACAAGTAGTGAATTTAAGAGTGGAAGTTTAATAGGTGA
Sequence 566

Sequence 567

ACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGGCAGGTCAAGCTTCGAC CCACGCGTCCGCATATTTTCATTACTTGACAATGTGGGATGGGTGCAATTTATTCCATCT TCACTAAAATAGAAGCAATTCCATAGGTACCATAAACCTATTTTAGGTACCACAAGGTGT CTTTTTACACAGCTCATTTGAATACAGGTGTTCTGAGAAGGGGTTTCTATTTTAAAATTA CCATATCAAAATAAATGTGCCTTATTTTTTTATAAGNCTTGTTAAATCAGTGTCCATATT ACTGTTTGGGGAAGG

Sequence 568

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGAGCGGCCGNCCGGGCAGGTACACAAACCAGATGTATGCANTGATGCCAAAAGTCATCTNAAAATTCCAAGCTGACCTAGTGCAACACATTTACACTTGGATAAACTATCACCTTGAAGATTTACTTTGTATACTTCAAAAGATCTGGTCATGAAATTTTTAGCTAATACATAAAGNGCCGAATTGAAATCCAGAATACAATAGCTNTGAAGGGCCGCTAGAGTGCAGATAACCAACCCATTCTACCTAAC

TABLE 1 93/467

TCAGGTTGAGATTGCTTTAGAACCTATCATTGGGCTTTAAAATGGTCCACAAAAAAACAC CTCATGGGCACACTTAAAATAGTTTGCATCCCACACTACAGGCTTCTCTGGAGGGATTTA ATACTTTGGG

Sequence 570

Sequence 572

TTAGGGCNATTGGAGCTCCCGCGGTGGCGGCCGAGGTGTACAAGCTTCGACCCACGCGT CCGCAAGTTTTCAAAATGTAAATACTTCCTCTGTTTAACAGTCCTTGGACCATTCTGATC CAGTTCACCAGTAGGTTGGACAGCATATAATTTGCATCATTTTGTCCCTTGTAAATCAAG ATGTTCTGCAGATTATTCCTTTAA

Sequence 573

GAATTGGAGCTCCCGNGGTGGGGCCGCTCGAGGCCGCTCTGACCTCTTTAAGGNANACT
TATTATGCTAATAGTTGATGCGCCCTTTTGCTGNANCAGTTACCATAGGTTACATGATAA
NTATATTGTTGNGATGATCTGATTNCCTGNNTNCCCCACCCNTGCAAAACAACAACAA
AAACCTTTACCAGGCTNTATAACANGGGGACCAAACTTGNTTTTGCTCATCATTGCCGGA
CG

Sequence 575

AGGTACTTACCCCAGACACGACGCCGCTTCACCATGATGATGGACAACAGGCAACTTTT
TTTTTGGAGTTTCAGCTTGCTTCCAACAGGGACGGTGAGTGTGAGGTTTATTCCCATTTC
TAAGACGATAGAAGTTTCAGCCTAAGCCGTATTCCTAGGTAAGCAGCTGGATTGCAAGT
TTTGTCTTGGAAATTCTCCTTAATGACTAAAAGTTAAAGAATTAAACAACCTAGCTGGGC
TTAAATTTCTTNCTTACCCATTAGAAGTACCCTTGCCC

Sequence 576

Sequence 577

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AGGTGTCGACTCAAGCTTTCAGATATAGGCATTCCAGAATCTTCTCTTTACGAGTTCACC TGCTAGTATAATCTCCACAACTTGAATGGCATTGGTTGTTCTGTAATTCCTGCCAAAAGC ATCACAAGTTGTACCTGCCCG

Sequence 579

CCGGGCAGGTTACAAGTCGACCCACGCGTCCGCTTCAGAATATCCAATTCATGTGAACTA CAGGAAATTATAGTTTAGATATTTTTAAATGATTTGCCTGTCACCGTATAACACAAGGGT GTCATGACCAAGCTAGATCTCTTTACCATATCATTAATAAAAGTCAAATTTTAAATTTGT GCCCAATTTGGCTGGGTGTGGTGGCTCATTCCTGTGATTCCAGCACTTTGGGAGACCT Sequence 580

Sequence 583

AGGTCGCCATCACACCCGGCTAATTTTTTTTTGTATTTTTTAGTAGAGACAGGGTTTCACCA TGCTAGCCAGGATGGTCTCAATCTCCTGATCTCGTGATCCGCCCACCTCAGCCTTCCAAA GTGCTGGGATTAAAGGCGTGAGCCACCACGCCTGGCCAGGAGATTCTTAATTATTTCTGA ACTCTATCAGTTTTGTATTAGGACATCTTATTTAATATTATCAAAAGATAGTTCCTCTTA GAGGCATAAATCAGTCAATCAACAAACAATAGGCAATCACGGACGCGTGGGTCGAAGACC TGCCCG

Sequence 584

AGGTGTACAAGCTTCGACCCACGCGTCCGCATTTTTCTGGTGTTCCCTCTTACGTGCACA CCCCTTGCTCCCCTTTGGGTTGACTTATAATCTGACTTTTGTGACAGATGTTAGGAGGTG GAGCAAAGGAATTTCAGACCAATCAGTTAAGAGACTGCTGTGGGGGTAAGAAAAAAATTA GCCTCTTAAAATTACTCTTATCAAAGGAAAAAAAGTTGGAAGCACATGATAGTATAACCA GAAACATGACACAGAAGAATTAAGGGAAGAACCTGCCCG

Sequence 585

Sequence 586

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Sequence 587

Sequence 588

AGGTACATTGTTAGACAAGTGTTTATCACTAATCTGGAATACATCATCTTCAATAAGGCT CTTGTTTTCCTCCAAGCTGCACCTGCTCACACTGCTCAGTTTTCTGTTAAGCAACCTGCTC ATTATAGTAGAGCACCCAAGGTGATCTGTTCTTCTGTTCTTCAGAAGTTCACTATTTCTTG TTGCAACAGGGCTACATGATTTTAAGATTCCTCAAAGTCAATACGAATTAACATTATTTT CCATTTCCATTCTGTATATCTTCACATTCCATAAATATAATACTCATGTATACGTTAAATTTCCTTATAAGTTCAACACACTTGAAAGCTAAAATAAAAGACTTCCTACTAG

Sequence 589

CCGGGCAGGTGGAAAGGTGGGTGGGGAGAGGGAGGCTTATTTGTTGCTGCAGTGTAACTA
AGTGAAACCTAATTCATATGACTCAAACTAAGGTATATTTGGTTAGATCTAGGTGAGTTC
TACTTTAGAGGAAATCCTGGTAACTGTTTGTTTGTTTGTAAGTTATAGCTGTAATTATTT
TCCCTGTATTCAAAGCCCCCAAACCCTGCATTCAGATACTATGCATTTAGACTTCCTTAG
GCAAAGTCAAGGCAACAAGCTGATGATTCTAAGCTATTATTCAAGGAGTATCTACCATCA
TAAAGGTGGTTTAG

Sequence 592

AGGGCCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTTCGACCCACGCGTCCGTTTA
CAATATGGTGACAACAGATAACTGTAAAAACTTCTTTTTCAAATAGAACCAGCAGGAGCA
TGCATGGAACACATATACCAAACATCTTCTGATAACATTAAACATTTTTAAAAGATGTT
AAATGTTCTTTTCATTGNGGTGCTTCAGATTCCTGATTCTAGAACTTGTGTGTGTGGAAC
CTGTGTGCTAACTATTCTGTTGGAATTTACCAGCAAAGAATTATCTAAGAATTTTCAAAC
TAAATGATGGGGGAAGGAACTAACATTTTTGCAGNCCCTGGAAATGTAAAATGTTGTACC

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Sequence 594

Sequence 595

CTATAGGGCCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTGCCAAAGCCTT
AACTTAGATTGTTACTTATGTTTCTAAATCTGTGGAAGCACATTTCCTTTTCTTCTT
TTCTTTTACTGTTAATATCCTTATTCTCTATTTTACCAGTGGAGAATGTTTAGTATTAAT
TTCCATTTAGCTCAAGATTCAAGAAATGCANAGTGCTATTTTTATCAAATTTCTGAAAGC
CTACTGTCTTCTGCTTTGGAAGTCCCACAACAGCTCTTTAATTTCCTTAAGCCCCACTTT
CCTCATCAGCAAGTTGGTGGCANTGGATCATANTAGGTTGCTGGGAGGATGAAGTGA
Sequence 596

Sequence 597

Sequence 598

Sequence 599

Sequence 600

AGGTCAAGCTTCGACCCACGCGTCCGTGATGCTGGCTTCCCGGTCAAAGCTGAGGAGTTT
TGTGGTGCTTTCTCAGGAACCTTCTGTCACGGAAACCATTGCACCCAAAATTGCAAGACC
TTTCATAGAGACTTTCCTCAGGCCCTCAAGAGTATTTGAGTATCTGGAGGAGGATGCCCA
GAAGTCCNCACAGGAGGGGGTGCTTGGGACCACACTGATGCTCTTGNCATTCAGACTC
TGAGAAACATGCCGCGTGATGAANAAACCATCCCAATTANANGAAGCTAGCTGNNTTNCA
TTGNAGCAGCTTTACCCCAATTT

Sequence 601

CCGGGCAGGTCAAGCTTCGACCCACGCGTCCGTGATAACTTCTCCTAAGTGCCAGGCATT GTATTACATGCTGGGAGCACAAAGATGAATAACAATAGGTTCACAGAAAAGATGAAT TGATTGAGAGAAAAAGAACCCTCCAGGAGCCCTCAGCGTAGTAGGGGGTTGGTGTTGGAG GGTGGAGGAATGGAAAAGGNCCTGAAATGCANGCAGAGAAATGATGAAACAATTCCNGGG GCTGCGGNGAGGTTANATGAATATCTTTACAGCAGCCTNGAAGACTGATCANGTTACTAT

TABLE 1 97/467

ACCCTCTCTTCTGTCCACGTGCATTTNA

Sequence 602

Sequence 603

ATTGGAGCCTCCCGCGGTGGCGGCCGAGGTAGCTTGAGTCGACCCACGCGTCCGTTCAG
ATCCGTTTCAGAAACGTGAGTCTCTAGCTCAGGAGATTTCCACAACTGTCCTTAGTAACC
TGATCTTATTCTCATGTTTAACCTTGGCAGTGGGAAGTTCTTCCTGGTATCCTGCCTAAT
TTACTGGAGTTGGCATTAATGCCATTTCCCCCTAAGGCGTGGCTCTTGGACCAGTATCAC
CTGAGAATTTGATAGACATAGACCCAGAGTTACTGAGGGCAGGTGCTCTGTTTTGGGGAC
CAGCAATCGGTGCTTTAGCAAGTNCTTTGGGTGATAGGGGTTNTGGAAACTACTGCTCTA
AAGCATNATCTGTTTTTTGAC

Sequence 604

Sequence 605

CCGGGCAGGTACANNTTGTGATGATTTTGGCAGCAATTACAGAACAACCAAGGCCATTCA AGTTGTGGAGATTATACTAGCAGGTGAACTCGTAAAGAGAAGATTCTGGAATGCCTATAT CTGAAATCAGAATCCTAGTAGTTTGTAGTTTGCCTCTTCCTAGAAGTTCAAGAGACTCAA GTCATAGGCTACAGATGTACCTN

Sequence 606

AGGTCTTCGACCCACGCGTCCGCAACTGTTGATCTAACTTTTCCACTTGAATGTCTAATT GGCAAATCAAACCTAACATGTTCCAAACGAGTTCTGAAGCACCCCCTCTGCCAAATCTAC GTCTCCCACAGCCTTCCCTATTTCTCTACCTGGTACCTGCCCGGGCGGCCGCTCGACCTG CCCG

Sequence 607

AGGTCTTGAGTCGACCCACGCGTCCGGAGATGTATACGCCACTATAGGAACTATAAGAAA
AAGTCAAATGGAAATCTTATAAATAAAAACCACAGTCACTATAATGAGGAAATACTTTGA
TAAGGTGTCAGTGAACTCAAAAATCAATCAATAGAAACTACAACTAAAACTCAAAGA
GAAAAAAAAAGATGGGAGATAATTATTTTTTAAGAATTGGTCATCAAAATGTAGCAACAA
GTTTGCCTTATCCTATATCATTTGAATTTTCAAAAAAATAAGCTCATTATACAATCTTTAA
AATATTTTGAATAGAACTGTTTCATGTGTTATTTGT

Sequence 608

AGGTCAAGCTTCGACCCACGCGTCCGGGGAACCCTTGTTCAGGTTCTTTTTAGGCAACCC AAGCCAAGACAACAAAGTAAGATAGAGCCCCAAATGTGGTCGTATAAGGTTTTTCAAAGA AAGTAACACTTGAGTTAGGTCTTAAAGTTTCACCTAAGAAACTGCCCAGGTGGACAAGAA GAAAGGGTGTTCCAAGTAGAAATAATAGCATGGACAAAGGCAATGTAGCAGGAAAAGTCT TCGTAAATTCAGGGAATTTCAAGTGTTTCACGATGGAAGGAGCAATAGAGTCATTTACTT GCGGTGGCAGGGGATGTTGGAAATGTAAACAAGAGTGAGATAC

Sequence 609

AGGTCAAGCTTCGACCCACGCGTCCGTGATGCTGGCTTCCCGGTCAAAGCTGAGGAGTTTGTGGTACTTTCTCAGGAACCTTCTGTCACGGAAACCATTGCACCCAAAATTGCAAGACCTTTCATAGAGACCTTTCCTCAGGCCCTCAAGAGTATTGAGTATCTGGAGGAGGATGCCCAGA

TABLE 1 98/467

AGTCCGCACAGGAGGGGGTGCTGGGACCACACACTGATGCTCTGTCATCAGACTCTGAGA TTACACCAATTGAA

Sequence 610

ACTITITITITITAGCTTGAGTCGACCCACGCGTCCGGGGATCTAGATCACGAGCG GCCGGCCGCCGGGCAGGTACGGAAGCCATGCACTTGCCTCTCCTTCAGAGCTGGGATTT TTTTCATTTTGCTGGCTGTGAGCACACACGCCCACAGGTGCCTAAGCCTCTTGTATG TGTGTTTTGAACTGTGTCCTCTGAGTTCTGTGTCTGGGTGCATGCTCTCCTCTTAGCGTG GGTCTCCTTCCCCTGTGTAGCACTTCACAATGTTAGGCATTTGTCTGTGATAGCAGCTGT TCAGTAATTTCCTACTT

Sequence 611

AGGTTTCGACCCACGCGTCCGGAATTTATCTGGCCAGGCATTGGTAGTTTACAGAAGTCT ACCAGATGATTCTAATGTGTGGTCAAGACTGAGAACTATGTGTTTAATTGGGTTCATTTC AAGAATACTGTAAAAATTTTATCTAAATACTAAATATCCATAAAAGAAACCTCGGTAATC AGGCCAGGTTTTTGAGTTTTTCCAGATTAGCCCAACTACAGGGGAAAGAGACTTTCGCAC TATATCCCAGAGTCTCTGCTCCTGCTTCCAGCCTCAATGCACTGGGCCTTTCTGCTGCCT TGGAGCACTTAGAGGGATTACAGGAGGAGTGATCTGTGGAGTT Sequence 612

TTAACCTTTCTATGTTAAATGAAAAACTTTGTCATTCATCAGGTCACAGAAACCAAAAA CTAAACAATGCAAAAAAAAAAAATCTAAAAATAAAAGAATTTTATATTTGAAGTTATTC TGGATATTCGCACCATTTTAGCTTCTGAAAAAAATGCAACTATGAAATGAAGACCTCATA TATTTTCATTTATCAATATAATGTTAAAAGTTTCATTCCACCGGGTGTGGNGGCTCACAC TTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGCGGATCATGAGGTCAGGAGATCGAGA **AAGGAA**

Sequence 613

CGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATTGTAGTTTTCTTAGCCATTTTTC AATAGTCTACACAGTGTTTATGTTTCCTTTTATTTGTGTATAGTGGAGTAGAGGGGAGGT TTTTTTATTCAAATAGAAGAAGCTAAAACTCAAATGCAATGTCAGATCTCANAATAAACT GACCCAATTTCTGAAACCCAATAAACACATTTCATTTGTAATATTCTTTATTATATAGCT CTATGAAAAGTAATTTGTGACTTTCGATCTTAAAAGAGAGATTTTAAAAATACACAGTAAA TTGAAAGAAAACTACTACATTTAAAACAGTATTTTCCTGAAAACATAGAATGAAAATGC AAGTATTTTGTGCATGGCAGCTGTTTTTAAGGAACCAATGTTATATATGGNGAATTTTGT GGAAGACTATGTCTCTTAAAATATTTCTTATAAAATANCATGGCTTTTTAATAGCTGGGA ATCTGANGNNGGATTTCCCATGAAGACCTTAAATGGCTNNGCAGGAATTATAAAAAAG Sequence 614

ACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATGCCTGTAATCCCAGC TGTTGGGGAAGCTGAGATGGGAGGATTGCTTGAGCCTGGGATACTGATATTGAGGCTGCA GCGGGCCGAGAATACCACTGCACTCCAGCCTGGATGACAGAGTGAGACACTGGCTCAAAA AAAAAAGGAAAAGGAAGAAAAAGTTTAAATCAATGAATGTTCTCATTTCTAATGAAAT AATGAAACATTATTGGGAGAGTTATAGTCATAATCATCTTACTGCACTATCAATTAAAAA ATACATCATTTTTTAGAGCACAATATATACCATAAAGAATTATTCAAATAGTCTAAATAT TACGATCAAATTTTTAATAGACTTTGTTACTTAAACTAAAACTGTATTAGTCTGTATTAG TCAGCTCAAGTTGGGATTCACACCTGTAATCCCAACACCTAGGGGGGC

Sequence 615

TAAATGTCTAACAACAGAGAATGGTTCTCTGTTGATACAAAATTATGATACATCAAAAAA GCGGTGGCTCACGCCTGTAATCACAGCACTTTGGGAGGCCGAGTCGGGTGGATCACGAAG

TABLE 1 99/467

TCAAGAGATTGAGACTACCCTGGCCAACACTGTAAAACCCCGTNTCTACTAAAATACAAA AATTAGCTGGGCCGTGG

Sequence 616

TTAGGGCGAATTGGAGCTCACCGCGGTGGCGGCCGAGGTACTGAATAACTGCCAATGCCA
TCTGCCTGTGGCCTTCTCAAGTTTGTCTGCACCTGTGGTTATCCTGACTTCAAACCCGGG
GAGACAGAGGCTAGAAGAGCAGACAGCTCTTGTGTATTCTCCTGTCCAGTGCAAAGAAC
ATCTGGAACTCTGAGCCCTAACCTTAAATGCAAGACCTNATCTGCAGGTGTTCCTNATCC
TTTTAGCCCCTCAGTGATGTAAGCAACAAACGTCACCCANCTCCTGGGGCACACTTNACT
CCCAGATGAGCTTGTCCTGGATTTGCAGGGAGCCTGGCTCCC
Sequence 617

GCCGGGCAGGTACAGATGGGGTTNCACCGTGTTAGCCAGGATGGTCTCGANTTCCTGACC
TCATNANGCATCCANCTCGGCCTCCCAAANTGCTGGAAATTACAAGGGCGTTGAGCCCAC
CCGCACCTGGGCCAGAATCTTACATATTTCTTAAACATCATTAAATATATTGTATTTT
TTACTTTTTTTTTGAATAGGGGTCTTGCTATGTTGCCCAGGCTTGGTTTTGAACTCCTGG
CCTTNANGAGATCCTCCCGCTCTCAAACCTCTCAAAAGCAATGGGTA
Sequence 619

AGGTACCCCATTTTATGCCATAGTCAGGTTTCTCCCTCAATAGCCCTTTGGAACTCTCA AGGTCCAGAGTGGCATCAAACCAACTGACACATGAGTTGATACATCATGTGCTGCCAACA GAGAAATTAGTCTGTGCCAAACTCAGCACAATCCTGCAGTTCAAACCAGAATTTCAAAAA

Sequence 620

ACCAAGATTTGAATCATGCTTTCAAAAGCTAATGTGAAGTTAGACATATTTGGTTTCATA ATCACAGAATTTTAAAAACACCAGGTCTGCAATATTCAGAAAATCACCATTAACGCTCTCT TGACACATACAATCAATTTCACTTTAGATCGCTGATTTTCTTAACAACTGATTTAGTTAT TTCTGAATACTGCTAGAAAATTCAAAATCTACAATTAAT

Sequence 621

AGGTACATCACCCTGCTGAGGGACATCCAGGACAAGGTCACCACACTCTACAAAGGCAGT CAACTACATGACACATTCCGCTTCTGCCTGGTCACCAACTTGACGATGGACTCCGTGTTG GTCACTGTCAAGGCATTGTTCTCCTCCAATTTGGACCCCAGCCTGGTGGAGCAAGTNTTT CTAGATAAGACCCTGAATGCCTCATTCCATTGGCTGGGCTCCACCTACCAGTTGGTGGAC ATCCATGTGACAGAAATGGAGTCATNAGTTTATCAACCAACAAGCAGCTCCAGCACCAG CACTTCTACCTGAATTTCACCATCACCAACCTACCATATTCCCAGGACAAAAGCCCAGCC AGGCACCACCAATTACCAGAGGAACAAAAGGAAT

Sequence 622

NCCGGGCAGGTACTGGATGACAGCAAGTGCACACATCAAGAGAAAGTTACCATTCAGAGG TGCAGTGAGTTCCCTTGTCCACAGNGGAAATCTGGAGACTGGTCAGAGGTAAGATGGGAG GGCTGTTATTTCCCCTAGGTCATCTCTTACATTCTAGTTCTGGTGCTCTCTATCTGTTTA AGACAAACCCTTGNGCACCTTTCTCCCACCCCTCCCTTTCTCCCTTGTCTCCCTTGAGAA AACAACTNCAGTTCTCTGCCTGCACCATGACTGTCGATACGCGGGGGCAGTTCGGCGGTC CCGCGGGTCTGTCTCTTGCTTCA

Sequence 623

TABLE 1 100/467

ATACTGAGTGGTGTAATGCAGTCACCTTGTCATCTGGCAAGAGGTGATCGATGGACACAA ACTCCTCCGGAACTGCCCCTCCAGCGAGCTCACTCTGAGGTTATCTGAACTCACATAGC TTGGGAAACCCAGCTGGGCACGGCAACATTTGCGTAGTGACCCTTCCAGTCATCGGAGC ACATGGTCTTCCACGAAGCAGCTGTGAACACCTGGAGCACGGCATTCTGACCACTCACCCGGACACAGCGGTACCTGCCCGG

Sequence 624

Sequence 625

Sequence 626

Sequence 627

Sequence 628

Sequence 629

TABLE 1 101/467

CCCCGCGGTGGCGGCCGCCCGGGCAGGTACATTATTGCTTCCTGGGAGAGCTGACCATGA GTCAATTGGCCCACAATAANTTATNAAATGAAAACCGGCCATCATCTGCATCTTATGAGT GCACGTCATCAGAGATGTCCACTCCAGTTACAAGAAAGTCCTGAGGGCTTTCTTGGAGCC TGANGGGCGCTGGAGGTGAGACCTGGAGGTGAGCAGGAGTTAACTAGGATGAGGGACNGG CGCAGCATACAGGAAAAGCTGCCTGGGGGAGAAAGGACCAACAGCAAAGACTGAGAAAAA AATGCTGTTGTGACCAGGGTTCAGAGCGGGCATGGAGGACTGAGGGTTCAGAGCGGGCAT GGAGGACTGAGGGTTCAGAGCGGGCATGGAGGGTTCAGAGCGGGCATGGAGG

Sequence 632

GCCGAGGTACTTCCCTGAGCAGTCGAAGTGGATGCCCAGACCAATGGCCAGNGCTAATAT NCAANGCAATGATCCCAATGACGATGATTGGAAAAAACTTCAATGGCAGCAGTGACAGGA TCTGTGCAGCAACAGCATCTGCATCTGGTGCAACAGGACTTATTTTCAAATCATCAAGGC CAAAAAGCGATCGGAATGAGAAGGGGGCTTCAACAGCAGCGGATCATTTTCCCCCATGG TGACTATTTCAGGACCTCTGACATCCGGCTCCGCCTCCACCTCTACCTCATAATTCCCGA GTCCCAAAAATGTAGATGGCACCACGGAAGAGATAGTAGGCCACAGTGTTACTGGCTTCC CATAAACACAGCCCTTTCCTGGCTCACACGGGCATGACCTAATTAAGAACCCCCGCGTAC CTGCCCGGGCGC

Sequence 634

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACAAAAGTGA AATCCCTAAGTCAAACTGTGGCTTATAAGCAGAAATCCTGGTTAGTATTTCAAAGTTCTC TTAGCGTTTTCTCCTGCGACTTAAAAAGACTTAAAAACGTGAAAAAGACATGGACGTAAGAC

TABLE 1 102/467

TGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACGGAGTAAAATAAAAGGGTCG
GATTTTGTAGGATTCTAAGGAAGAGGCAGTGTGCTCTGTCCACAGGCTGCAAGGTGAGAA
CCTAAAAGAATGAGATATATTCCCATTTTGGAATGGCAATCAAAAAGAGGATCTCTCTGT
CAAGTCTTTACATTAATGCTGAGTAACAATCTCAAAAGCCTGCCCATTCCCCTTTAGACA
CATGTGGCAAAAGCAGAACTGAAGGAATGGCCAAGGGGCTTGAACAAGTAGAGAGACCGA
CAGTCTTTCAAATTTCAGGGAACCCCAGATACATTTTGGGGGAGCCACTGTTTTCCCATT
TTCCTGAAAAGTTCTTGCAGGTATAAGAAATAGGAATAGAAATTGAATAGGTTCTGGAGC
CAGGGCTACAAAGGCCCCAGCTCTGATCTGTTAGACTGAAAACCACACATCAGATGAAAT
TATATNCACAAAAAGGAGAGTCCTTAAAAACAGCCATTTCGGTCCCT

Sequence 636

AAGAGCACGTATAGCATGGGGGAAAGAACCTAAATGTCTCTCTGTCCTGTGAGCTGGTGA
AAAACCCAGCATGAGAACGCAGTGTCAGGTGTGGGACTCCTTCTGCCCCTGCAGTGGGTG
TTACGGGCGGTGTGCCCTGGCGAGCAAGCTTTGATTCTTGGTTCTTTGAGCTCGTTTCAG
AGGCTGAGTCCCCACATCAGCTTTAGTTCTTGGACTTCCCTGTATTAAGCAAGAATTAGG
AGAATGGCTGTCCCTGCAGGCGCCTCCCGTAAATCCTGAGCTCTCTGGCGCAATCTGAAA
CTTCTCTCTGTTTTCTTTGGCTGTATCAGCCGAACCAGGAGAGGCC
Sequence 637

CCGGGCAGGTACCAGGAGAGATCTGAGACANGGTATGAAGTAAAAGATTTAAGATTGGAA GTGGAGAGTGTCATGGACCAGTGCCTTTCGGATGGGTGACTTCTGGAATTCTTGTTAGGC ACAGCGGAGGTTGGTCCTGTGGGAAAGGAAGAATATTTCCGGGGTGAGGAGACTTCGGGG TGTGGGCCGGGTGCCTTTTTAAATTTGGAATGGTGTATACAATAGGGAAAGGATGTTAAC TTTGCAGCAGCGGGGATGGTGAATATAACCTGATAGGGACCCTTCCATTTTGTTGGAAAG GGGAGGAGGGGGTGTGCTACCCAGACCCAGTCTCCTGGNTGTAAGGGTAAGAAAGTGAATT GGGAAGAATCCTCAGG

Sequence 638

Sequence 639

AGGTACCACTTAACAAGGGTTCTCAGCTGTGNGGNCACTGGACCACTGGGATATGCTGAG CTATTGCTTAAACACTGACTTAAATAAAACAAATATTTTAAATAATGAGAATGCTACTGT AATTAGAAGGCAATCATTTCAAAGTCTANATGGAGGCCAGGGGCGGTGGCTCATGCCTGT AATCCCAGCACTTTGGGAGGCCGAGGTGGGTGGATCACATGAGGTCAGGAGTTTGAGACC AGCCTGGCCAGTATGGTGAAACTCCATCTCTACTAAAAATACAAAAATTAGCCAGGCGTG GTGGTGTGCACCTGTAATCCACTGAGGCAGGAGAATCACTTGAACCCGGGAAGTGGAGGT TACAGTTGAGCTGAGATAGCACCACT

Sequence 640

AGGTACAAAGGTTCAGTGGTGAGAAGAGGGGAGCAAGGCCTTTGGAATAATGAACTCCAGT TGTTCCTCATAGGTGCAGCAGAAATAGCGAGAGGTCAGGATTATGGAGATTGGTAAGGCG AGATCATCCAAGGGCCTTTTGCTTGGTAAGCCATTTTACTTTAATCTTGAGTGCCATAGG

TABLE 1 103/467

Sequence 641

AGGTACCTCGTTTCTGAGGATCAANACCTNAGNGACCGNGTGTGTGTGTGTATTTGTG
TGTGTGTGAGTCCTATTTGGGCCCCGCCTTTCAGCCCTGTCTTGCAGC
Sequence 643

Sequence 644

CGGGCAGGTACTAGTCCAGGTGTGAGATGAAGGGGGCCTGGATGAAGCAGAGGGTGAGAG ACAAGGAAGATTCTGAGGACCTTGTGGCTAGATGTGGGGGTTAAGTCAGGTTCAACTCCT AGGCTGGATGAATTGGCAGATGGCACATGAACTACAAGAGAATGGAAGGCAGAACCTATT TTGTGGGCAAAAAATAAATTACATTTTGCAATACTGAATTGAGGGGCTTCTTGGAAGTCC AGGTGTAGATGTCTTACAAAAATAGAATATTCTGGGCTGGGTGCAGTGGCTCACCCCTGT AATCCCAGCACTTTGGGAGGCCAAGGTAGGGGGATCACCTGAGGTCAGGAGTTCGAGACC AGCCTG

Sequence 645

GGNCACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTCAC
CAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCCCAATTTGGA
CCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTGGCT
GGGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATCAGTTTATCA
ACCAACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCAACCTACC
ATATTCCCAGGACAAAGCCCAGCCAGCACCC

Sequence 646

TABLE 1 104/467

Sequence 648

Sequence 649

AGGTACTAGTATGAAGGAAATAATATCCACACACTGATACTGGTCCAGCNGAAACCAAGA CCGCTCCTGGTGCATTAACTTTTAACAGAGCANGGACTCANTTCTCTGAAAATAGTGCCA TAAAACATGTGCTCCCAGAAGAATAAATATTTGGCTTGCTAGAATTTCTGCNGCTTTTNT GTAAAAGTTGATTATTCGGTATTAAAGAGGAGTATCAAATATGNGTNNATGNANNAAAAA CTTGGAAANAGTANNGGACCNNGGCTTATCTCNTCATTTTCATTCTGCACACTNCAANTC ANTCNTTTTCCCATCTTNNTTCCCNTCTCTGNAATTTATCACCCTCCCCCTCT Sequence 650

Sequence 651

TABLE 1 105/467

ATTTTTNNGNCCAAAAATTNGGCAAAAAAAA

Sequence 653

TCCACCGCGGTGCCGCCCGAGGTACGCGGGGGCCCTTCTATCTCAGGATGTTTGCACTT
GCTATTTCCTTTAAAGGCTCATCCCTAGATATTTGCATGACTGGCTTCCTAATTTN
NTGTAAGCTTTTGCTGAGAAGTTACTTTACCAACTGTCATTGAGGTTTTCCCTGAACATC
TTAGGTAAGATAACAAGCTCCCCTCCTTTTCTTTCCTCACTTCTTGGTATTCCTTATCTC
GTAACTTTTTTTTTNGGGGGGATNGANACTTNCGTNTTGNTTTTGTTGGCCAAGCTTGGA
GTGCANNGGGTGCANTCTTGGCTTNACTGAAACCTCCACCTCCCGGGTTTAAAGCGATTC
TTCTGCCTTNAGCCTNCCGAGTAGCTGGGACTACGGGCAAGTGCCACCACACCCAGCTAA
TTTTTTGTATTTTTAAGTAGAGGGTGGGGTTCACTGTTTAGGATGGTCTCTATCTCCTGA
CCTTTTGGGCCACCCACCTCGGCCTCCAAAGTGCTGGGATTATAGGTGTGAGCCAGTGCN
CCCGGCCTCTCATAATTTTCTTAAATT

Sequence 654

CNAATTGGAGCTCCCGCGGTGGCGGTCAGTTNGTCTTAGAGATACCCATGAGGTCACCT
ACTCAAAATGGGGCTCAGAGTAGCCTTGTCCCATTCTTGTCCAGTGGGCGCAGCTACAGT
CTNNCTGGNNNGGAGTGACTGGAGGCTGTCCCCACGTCCCACTTCAGTGAGGCATTCATG
TGCACCCAGCACACTTTCTAGCTTTATTTGCCTGGAGGGGAAGATTCTCCAGAACCTTGT
TAAGATGCACAGNGNGGGCCCTTGGACTGGCAAGTGTGGCCTTNGGCAGTCCCTNGGAGC
TTGTTAGGAATGCAAAATNTTAAGCTTCTTCCTACTGNATCTAAAGGTTGANTTTAAACA
AGATCCAGCTTGTTTCGTTTCACATGAAAGTTGAGGCACACTGCTCTAGAAAGTTCTTTT
ATCTTTACTGGCCCACCAAAGTAATCAAACTTTGNGAAGTACCCTCGGNCCGCTCTAGAA
CTAGTG

Sequence 655

Sequence 656

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Sequence 658

Sequence 660

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCTTTGAAGGTGAGCTTTGAAGATGCAACATGAATTTGACAGTANAGATGTAGGGAGGAAGGAAGGCAGGACAGGCCAGACCCCCACACCCCCTACAAGACCTGCCSequence 661

ACTTAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCCCCGGGCANGGTACGCGGGGACT TGACTTAAACTCTGGGGCCCGGGAGGCCGCCGGTTTTCTCCCCGCTTGCCGGGGTGGTCC TCTTCCCTTTGTCGGACCAAAGAAGTAAACACTGTGTGGAGAGGGACTGACGTGTTTGGA GGGAAATGGGAATGTACCT

Sequence 662

TABLE 1 107/467

Sequence 664

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGGGCAGGTACTGCTGGTTTTCTGGTGTTCCTACAAGCTGCCTAGGTCTCTTTTGTTCTCAGCAGTTCCCAGGCATGCAAAAGTTGCCAGTTCTGTCAGCATTCCAAGTCAGGTAAGACAGAAAGCCATCTCTTAGGCAGTCCCCAGAAAAGCTGAAAAGGTTGGATATACTTTCTACTCTTTTCTTCATGAGAAAAGCCATGTGGGCATTTCCCCAATAACACTGAGTTCTGTTGTCTCTGTCGGCTGTGCTGCAGGTTCTCAGGGTGCTGCAGTTCTCAGGGTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAGTTCTCAGGTTGCTGCAG

Sequence 665

CTTAGGGCGAATTGGAGCTCCCGCGGTGGCGGTAAGATTTCCTGAAGGGATCCATAGCC
AAAACATGTTTGAAGGCCACTGGGCTCGCTAACTTCTAAAAGCACCCCAGTTCTAGCAGA
CATCCTAAGGAACATTCCCAGGAAAATTCCAGCCTAGAACCTCCTGGGGTCTGACAACCT
TAGAGAACAGTGCTGGCTTTGAATGGGCTTGGGGGCAGCCTCGAAACCCTCTTTCCAGTC
TCCATGCAGGCAGGGGAGCTCCTTAAGCAACACATAGGACATTCTGGGAGAAATGGGAT
CCCCAACACAATGAACACTATAGATTTTAATGGTCTATATGGTTAAATACACAAGGCCCC
TCATTTCCAACCCCGCCTGTTCATCTGATTCATCTGTACCTCGGC

Sequence 666

GGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTCAGACATTCCCCCAGTGGCT
GAAGTGGCATATGAATTATGAAGTTGGATCATTTGGAATGAAATGTAAGAGAATTGCCAAG
GGCTCCTCCTACTCCAGAGAGGAAACCTCATCCAGGGCCATGAAGCCACTTCCTCACCAT
CTGTGTGCTGCTTAAGCTAATGCTGCGGGAACCATGGTTCCTTGGGAGGAATCAAGCTGA
CTCTTGGCATGAGATTCCTGCCTTCCTAGGGTTGAGAGCGGCACTGCCATGGCTTCTCTG
GACGACCCAGGGGAAGTGAGGGAGGGCTTCCTCTGCCCTCTGTGCCTGAAGGATCTGCAG
TCTTCTATCAGCTTCACTCACATTACGAGGAAGAACACTCAGGGGAAGGACCGTGATGT
CAAAGGGCAAATTAAAAGTAAGAGGCGAGGACCTTGCCTACCCCCTGCTTGTCGTTGAGA
GCTTTAACTCACNGGATAGTTCTTATCACTTTTGGTGGTGGCACAGGNATATGATAATTA
GTAGTAGCCAACAGATGACTAGTNGTTGTCATGTGCCAAGCGTTTTAAAAGTTNCCTGTT
ATTAATTTCATTA

Sequence 667

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGCGGGGAAGAG
AAAGCGTGAGGGCTGGGCCTGCGGCGGGCTTTAGGGAGTGCTCCTGGCTGTGGATAGAT
CTGCTGATGAGTCCAGGCCCCGGTCCATTCTCCTCGCGCTGCAAGGATGCTCCTGGGATT
TCGGAGAGGCCGCAGGAGTCATTTCAAACACATCATCCATGGCCTTTTACCTGCAGCCAG
CGTTGCTCCGAAGGCAGCTGTGCCACGCACACCTCCTCCCCGCAGCCCCAACCCATCTCC
AGAGAGACCAAGATCTGCTCTGGCAGCAGCCATTCTGGCGACACACTTGAC
Sequence 668

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTGGATAGGAGAGGAGGAGGG CTGCCAGCTGAGTAGCCAGAATCAGGCAGACGTGGTAGCAGAAGTCAGAGGCCGAGGGA ATCAGGGAAAGGAGTTCAACCATGGAGGACCTTGCTGGCCAGGTTAGAGACTGTGGACTT TTGTCTGGGTGAGACAGGAAGTCACTGGAGGGCTGTGACAGAGCTCTGAGGCTGTGAGGC ACTGCTCTGTCAGTGCCATGAGTGGGGAAAACAGGAGCTTGCTGCACTGGTAGAGACCAC AGATAATGATGACTTGGACAGAGCAGCTGGGAGAGAACTAGTTCAATAACCCTAACACGC CTCTCCATTCTGCATTTTCCCTAAAAATGTACCTGCCCG

Sequence 669

CCGCGGTGGCGGCCGAGGTACCTGCCCTATCTTGCTGAATGTTTTATAATCTAATAAAAC TCAGATAAAGACCCAGATGTCACACCTGAACAGGAAAAGCTGAAAGGAAAAGATAATTAA AATATAAATCAACAGAATCAAGATTTTGAAAAAGACCTAGAAAACTTGAAGGATTACTGAA

TABLE 1 108/467

Sequence 670

CCGCGGTGCCGCCCCGGGCAGGTACGCGGGGAGGTCATGCCCGTGTGAGCCAGGAAA
GGGCTGTGTTTATGGGAAGCCAGTAACACTGTGGCCTACTATCTCTTCCGTGGTGCCATC
TACATTTTTGGGACTCGGGAATTATGAGGTAGAGGTGGAGGCGGAGCCGGATGTCAGAGG
TCCTGAAATAGTCACCATGGGGGAAAATGATCCGCCTGCTGTTGAAGCCCCCTTCTCATT
CCGATCGCTTTTTGGCCTTGATGATTTGAAAATAAGTCCTGTTGCACCAGATGCAGATGC
TGTTGCTGCACAGATCCTGTCACTGCCATTGAAGTTTTTTCCAATCATCGTCAT
Sequence 671

Sequence 672

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACGCGGGACACTGGTGGGGGAGAGTCCGACGCGCCCTGGCTAGGAGCCCCGACGCCCGAGGCCTCTACGGACCTTACTAGAAAAATGAAACCTGATGAAACTCCTATGTTTGACCCAAGTCTACTCAAAGAAGTGGACTGGAGTCAGAATACAGCTACATTTTCTCCAGCCATTTCCCCAACACACTCCTGGAGAAGGCTTGGTTTTGAGGCTTCATGCCAGAAAGGGGAATGGGGAATGGCTGCTTAACGGCATGTNTTTT

Sequence 673

Sequence 675

Sequence 676

AGATAATAACATCTGATATCCACATGGGGTCTGGAGGNGCAAGCCACCTTCCTTTCATCC

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PCT/US01/09126

CACGGTCTCACAGCAGCCCTGGAAAGAGGCTGCTCTCTGTTGGAGGCTAAGGGCCAGTGT TGGAAGGAGCTCGGGTGGAAAGTGTGGTCTGCATGAGGGGCTCCCGTGAATAGAGGAGAG GGGTGGCNGGTACCTGCCCG

Sequence 677

Sequence 679

Sequence 680

AGGTACAAACTGGCTTCTTCTCTTTGTCACCAGCACCTGCTTCATAGTCTCTCTGGAGTG CCAGGAACGGGTCATTTAGATTAAATCTCCCATACCGTTCCTGGATAAATACCTCCTTCC TGCGAGCCCGCAGGGCCTCGATGACAAGGTCTCTGGCCTCCAGCTCCCCTTCCATCACGC TGAGGAGCATCCGCAGCTCGGATTTACTGAGAGTATCCACATCAAACTCTTTTTTCAGTT TTACAAGTGGAAATTAAGCAGTCCTCCCCCGTTTCTCCTTCCATTGCCAGGCTCAGCT CCTCTCACCCCAAGTACCTGCCCG

Sequence 681

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAGGTGGAAAGTGAGGTGGTTT
TATTTCTAGTTCACCATTGTCCTTAGGCTGTATAGACCTCTGGAATCCCAGCTTATGTGG
AGAAGGTATCCTGTTAGACTTCCCTCTTTGGTCAGCACTGGGCCTTAACTTCTGGCCCC
TCAAAGCTGCTAAAACTGAAGGCCAGGCTTGCCTGGCTTGGCAAAGGACGTCGGGCAGAA
GCAGCTTCTCCTCTCTCTTTTTCTCTGTTTCCCCTCACCATAGGCTTTGGCCTGGGAG
TTTTCCTACA

Sequence 682

TABLE 1 110/467

TNAGAANTNAGTAANCTTAAGGCTTNAAGAATCAACAGNGCCCCTTTGGGNATTAAGGGCCATT

Sequence 683

Sequence 684

Sequence 686

Sequence 687

Sequence 688

NGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGGGGGCCATTGAGACTGCCATGGAAGACT TGAAAGGTCACGTAGCTGANACTTCTGGAGAGACCATTCAAGGCTTCTGGCTCTTGACAA AGATAGACCACTGGAACAATGAGAAGGAGAGATTCTACTGGTCACAGACAAGACTCTCT TGATCTGCAAATACGACTTCATCATGCTGAGTTGTGTGCAGCTGCAGCGGATTCCTCTGA GCGCTGTCTATCGCATCTGCCTGGGCAAGTTCACCTTCCCTGG Sequence 689

TABLE 1 111/467

CCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTGCTATGAATCTCACA GATGTAATAATGAGTTAAAGAAGCTAGGCACAAAAGAATATTACTGTATGATTCCAATCA TATAAAGTTCAAACCAGATCAAACTAATCAATGAACGAGGAGTCAGGATTCTGGTTATAT TCAGGGATAGTGAAGAAGAGGGCTATAAGGAGGGTGTCTGGGTGCAGGTCATGTTCTAG ATCTTGATCTGAGTGGGGGTTACATAGGTGTATTCACTTCATGAGAATTCAGAGGGCTGC ACACTAATGATCTGTATAATGCTCCTCTATAGTATGTCACACTTCAAAAAAAGTTTACAGA AACAGTTCCTTCAAATTTTCACAGGGCCTAAGAGCTAAAAAACGCAGCCCCAG Sequence 691

NCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGGGGGCCATTGAGACTGCCATGG
AAGACTTGAAAGGTCGCGTAGCTGAGACTTCAGGAGAGACCATTCAAGGCTTCTGGCTCT
TGACAAAGATAGACCACTGGAACAATGAGAAGGAGAGAATTCTACTGGTCACAGACAAGA
CTCTCTTGATCTGCAAATACGACTTCATCATGCTGAGTTGTGCAGCTGCAGCGGATTC
CTCTGAGCGCTGTCTATCGCATCTGCCTGGGCAAGTTCACCTTCCCTGGGATGTCCCTGG
ACAAGAGACAAGGAGAAGGCCTTAGGATCTACTGGGGGAGTCCGGAGGAGCAGTCTCTTC
TGTCCCGCTGGAACCCATGGTCCACTGAAAGTTCCTTATGCTACTTTCACTGAGCATCCT
ATGAAATACACCAAGTGAGAAATTCCTTGAAATTTGCAAGGT

Sequence 692

Sequence 693

Sequence 694

GGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTGGTCTCTGTCTTTAC
AGCTGAAGCATCAGAGGATGGAGTGACCAGGCTGGTTCCAATGACAGTTATACGGCCATG
GGGAGTANACATGGAGTCTAATTCAGTGCTTGAGGCTAAGAATGAAGTTGTATGCATTGT
GGAAATTGTTCCAGGAGATCTTGCAACTTTCAAGTTTGAAGTCATGTCTGTAGACAGTCCA
GGAATNTGATGCAGCTGTGGAAGACCAGGTGGAAGGGTGTTCTGTAGAAGTTGTGCGCCT
CTCTGTGGCCGGGGTGCTGTCCATGGTACCT

Sequence 695

ATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACACATGTATCANG GAAAAGAAAACGTTATTTGTCCCACAGATGCTGCTAGGAGCAGCTACCCCAAGACAGGCC TTGCACCTTGGGTCATGACAATGCGTGGCTACTGAGAGCTGTTGACAGAGTGGACAGGGC CCAGACCAGGACAGTCTCTCTAGAGGTCTTCACCTCCTCAACCGTAACTTAATCAGCCCC

TABLE 1 112/467

ATGCCGGGCTAGCCCATGCCACAAAGGCTCAGAAATGCCCTGCAACATGTGGGACACCT GGTAGTATCTACATAGGGGCCAGCATCCATCCCAGCTGCTGGGGGTGGCTCAAGAGCTGT GAGGGACACCCTTTCCTGCCTGATACCGTGGACCAGTTTGCAAAGAGCTGACTGTCCTGC TAGGCCCA

Sequence 696

Sequence 697

Sequence 698

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCATCCTATGCAGNCATNC
TGTNAGNACCCATTCCATTNTNCTATCCCTGGNTNGCTGGTGTCAATACTNTNAAGCGAN
TTACTGCNGGNGCTCTNNTTTTTCCCTCANAGATACCNNGTTGATTTCTTTGATTCTCTC
CATCTCTACAGGCATAATAACTCCTAATATTTAAAAACNCTGTAGAGGGATGNANNGAAG
CTGNGGNGAGAGCCCNTGGGCTTTTCNCNTGGGTNAAGATGCACATTCCTGAAAATTNTG
GGCCTTGGCTTAAGCTGNACTAGNGCCGGCCACTCAGCTGATCTCACTAGCGTCACCTGT
CGCAATGGTGCTGAAGCGCACTNCCNAGAGGCCATAAGGCAAAGCGAGAGTNCNTGGCTA
TNGACTGGANCCCATTTAAGCAAAAAAACATGCCTCNCGNANGACAAATTCNATCAACAA
AGGGNGGGCAATACAGGATCTGTACCTGCCCGGGCGGNNCGGGCANGAACCTTTTTTTTT

Sequence 699

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCCAGCCCGCCACCCGGCTT
GTGTGTCATCCTGGGCCCAGGCAGGTGATGATGCCAAACACAAGGCCCAGCTATGTAACC
AAGTAAAAACTTTCATCAGAATGCCCATCTTTGTGACCCACAGCCCATTGTCAAGAGCCT
TCCCTGTGCCAGGAGTTCAGCAGGTTCACCTCCGCCTCCACTAGTCACTAAGACACGGAT
ATTTTAAGAATTAAAAGCCTCCACAAGCCAGGCACAATGGCTTACACCTATAATCCCACA
ACTTTGGGAGGCCAAGGTGGGAGGATCACTTGAGCCAACGAGTTCGAGACCAGCCTGGGC
AACATAGCGAGACCTTGTCTCTACAAAAAAAATTTAAAAGTTAGCCAAGCATGGTGGGGCA
TGTCTATAGTCCTAACTACTTGGG

Sequence 700

TABLE 1 113/467

CGGCGCCCCTCTAGAACTA

Seguence 701

Sequence 702

Sequence 703

NGGTTAANTGCCGCCNCTTGGCCGTAATCATTGGGNCATTAAGCCTGGTTTTCCCTNGTG

TABLE 1 114/467

TGAAAAATTTGTTATCCCGCTCCACAATTTCNCACACCAAACATTACCGAAACCCGGGA AGNCAATAAAAAANTGGTAAAAAGCCCTTGGGGGGGGTGGCCCTTAAATGAAGGTGGAAGC CTAAACCTCAACAATTTAAATNTTGGCGGTTGCGGCTCAACTTGGCCCCCGCCTTTTTNC CAAGANGCGGGGGAAAAA

Sequence 707

Sequence 708

GGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTGAACATCCATGGCAGACGCTATT CTTTCCCTCTTAGAGATGCAGACACTGAGGCTCAGAGAAGTTGTCCCGCACCCAGTATGT GATGGAGAGGGTAGAGGGTAAAAACATCAACTGAAGGATTTAGCATTTGGGGAAGAAGGAA GAAGCCCAAAATGGAGTAGATCAAAGGCTCCCCCGTGAACAAATTTAAAATTAAGGAGAA AGAAGCAGAATTCAGTCTTCTCCACACCCATAACCAAACAGCTCCTATGAAGGCACCAAG CCTGACGCTCATCCCAATAAAAAGGAACGATCTGGAGAGAGGGGCAGCCGCTGGTGACAA GAGAACCCCCCAGGCAGCCTCGTCATCTGGCCAG

Sequence 710

TABLE 1 115/467

Sequence 713

AGGTACCGTGTGAGCAGGTGGCGTTCACCAGGGGTGAGACTTTATTGACAGTAAGTTGCC
TCTGCCAAAAAACGCCCTCATATGTCTGCTGATGTTTGAATTNCNNCCNNATGGCAGGAG
GTTTTTTGGTCCTCCCCAGNTTTAAAAAAAAAATTGGTTAAAAATAACCTGGGTTTGGTTN
TTTCTTTTGNTATGGGGAAGGCCCTTCCAAGNAAGNGGAAAATAAANAAAAAAGTAATTA
NANCCTTAACCTTCCTTAAGGGGGAATTAATTGGTAATTTCAAAATTTTTTGGAATGGCC
TTANCTTTTNTTAATTTTTTTAAATTTTTTAAATTTTTTGGGANGGAAACCAAGGGGGGGG
TTTCCTTNTGGGCCTTTCTTGGTTTGGCCCCCCAGGGGGCNTGGGGNANGGTTGGCCAAGG
NCCAATNTTTNNGCCAAAATTTCCAAACCAAGGGCCCTTTCNAACCTTTGGGCCAAGNTC
CCCCTTTCAAAAAACCCCCTTTCNNCCTTGNTTTGGGCCCCCCAAAA
Sequence 715

CCGCGGTGGCGGCCGAGGTACCGTTTTATGATGATAACATAACTTTAATGCTCCAACCTG
AGAAAGATAAAATAGACTAAGATGACCATTGAATGCAAACAGAAAGTTCTAAATGAACAA
TCAAGNCAGGACCTGGAAATTTCAGGTCCCTGGTGGTTGGAAAANTAAATTAAAATTAAAA
ACCAANTTTCTTGGTTTTTCCAAGGAAAAANTGGNTAAAAAAAAATTAAGGTNTTTAAAAT
AANCCCCAGGGAAAAATTTCCAAATTCAAAATTATTAAAAAAGGCCTTAAATTAAAT
ATTTTTTGGCATTTCNAAGGCCCCAAACCTTAAAATTGGCCTTANCCAAAATNGGTTTTT
GGGTAATTAAACCAGGGCCAAATTTNATTAAAAAAATTCC

Sequence 716

Sequence 717

CCGCGGTGGCGGCCGAGGTACTACAATAAGGACAAATATTCAAAACATTCTGTTAAGTAA
AATAAGACAGTCAAAAAGGAAAGCTGTATAATTACACTCATGTAAAAATATTTAGTCCAA
CNCTCACAGGANAACCAAAGGTGGTCAATAGGTTCCTCAAGCCAGGTGGCCACCCCAAAG
GAATGGTTAAACCAAGGTTCTTCCTTCNGTTAAGGTTCCTGGAAGGAATTAAAACCAATT
CCCCAAGGAGGTTTNCTTTTTGGTTTTCCTAACCCTTCTTAAAGGGGAGGAATTTTAAAG
GGGAGGTGGTTAAAAANCAACCAAAAAAGGGTTTGNAAAGGGNTTTTGGGGGAAGGNTTT
GGGAAAAAAANGNTTTTTAAAGGNA

Sequence 718

TABLE 1 116/467

Sequence 719

Sequence 720

CCGGGCAGGTACCGCTGTGTCCGGGTGGTGGTCAGAATGCTGTGCTCCAGGTGTTCACA GCTGCTTCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTGCGCAAATGTTGCC TGTGCCCAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAGAGTGAGCTCGCTG GAGGGGCAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTCTTGCCAGATGACAAGGTG ACTGCATTACACCACTCAGTATATGTGAGGGAGGGGATGTGCCTCTGGCCACGTGGTTAC CTTGCAGTGCACAGCCTGTGGTCATAGA

Sequence 721

CCGGGCAGGTACCGCTGTGTCCGGGTGGTGGTCAGAATGCTGTGCTCCAGGTGTTCACA
GNTGCTTNGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTGCGCAAATGTTGCC
TGTGCCCAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAAAGTGAGCTCGCTG
GAGGGGCAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTCTTGCCAGATGACAAGGTG
ACTGCATTACACCACTCAGTATATGTGAGGGAGGGATGTGCCTCTGGCCACGTGGTTAC
CTTGCAGTGCACAGCCTGTGGTCATAGAAGGGGCTACAGCTCACGCATCGTGGAAA
CATGTCCTTGCTCTCCAATGGCCCTGGCAGGCCAACCTTTAGTTTCAGGGCTACCACCTG
TGCGGGGGCTTNTGTCATTACCCCCTGTGGATATTAATGCTGCACACTGNGGTTATGACT
TGTACCTTCGGCCGTT

Sequence 722

GGAGAGGAAATGTGTAGGGGTGAGGGATGATACAAGAAAGCCAAATCCTCATCTTCTATA GTAGAGAGTCAGCGGATAAAACCTAAAAACAATACATCAAGAAATACTTACACTTATGGA AGGAAATACCAGAAGTTAAAAGGGGTTACTTCTGGGACATCAGACACCAGACTGCAGGGA AGGGCTGCCTCTTGTATTAACAAGCTTCCAGTATAATTTGCTTTTTAAAAAATAGGTCCAT GCATTATTTTAATAAAAATTANGCTGGGCGTGGTGGCTCAGGCCTGTAATCCCANCACTT TGGGAG

Sequence 723

GGGGCCATTGAGACTGCCATGGAAGACTTGAAAGGTCACGTAGCTGAGACTTCTGGAGAG ACCATTCAAGGCTTCTGGCTCTTGACAAAGATAGACCACTGGAACAATGAGAAGGAGAGA ATTCTACTGGTCACAGACAAGACTCTCTTGATCTGCAAATACCGACTTNATCATGCTGAG

TABLE 1 117/467

TTGTGTGCAGCTGCAGCGGATTCCTCTGAGACGCTTGTCTATCGCATCTGCCNGGGCAAG TNTCACCTTCCCTGGGATGTNCCCTTGGACAAGANACAAGGGAGGAANGGCCTTAANGAT CCTANCTGGGGGGGGA

Sequence 725

TAGGGNGAATTGGAGCTCCCCGCGGTGGCGGCCCGGGCCGGTACCCATAAAAATTAAA
AACTATTTTAAAAAAATAAATTCCATTTGAGCCACTCCTTCAAACCACCCAGAGTGGGTAG
ACGTCTTTCGTGCCTCTAAGAAGCCCCATCTCTATTCTGCGTCTCACCTTGCAGGGCTGC
TCATCTGAATCCTGAAGATGGTGGACACCCATCTGCTAGGACTGAAATGAATAGGACAGA
GGGAGGTGCAGAGTGAATGGACCATACTACCTGTCATCTTGGCAACGTGTGATTGAATAA
AACAACTTCTTTAGAAGTTTGATAGAGTGATTTGATAATTTACAAGTGATCATTT
CTTTTTA

Sequence 726

Sequence 727

Sequence 728

Sequence 729

Sequence 730

TABLE 1 118/467

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACACTACACCTGGACAAA TACTTTTTTGTGAAGNCAGGTAAAGCCTTTGCGTGCAATATAGCATCTCTATGCAATGCA NCAACTCCTCGTCTATCGCTÁCAGTAAGAAAACAGCCACGGGTCAGGTTGNGGCTCAC ACCTGTAATCCCAGCACTTTGGGAGGTCNAGGTGGGTGGATCACTTGAGGCTAGGATTTT GAGACCAGCCTGACCAACATGGAGAAACCCCATCTNTACTGAAAATACAAAATTCCCGGG TGTGGTGGCNGCATGCCTGTAATCTCAGCTACTCGGGAGGCTGAGGCAAAAGAATTGCTT GAATCTGGNAGGCGGNCGTTTGNNGGTGAGCCAAAAAATCGTGCCATTGCACTCCAGCCTG GGCAACAAGAGCGAACTTTCGTTTCAAAAAA

Sequence 732

Sequence 735

GCGAATTGGAGCTCCCCGCGGGGGCGGCCGCCCGGGCAGGTACTACTGTGTCCTTTAGAT CACTCTGCCTTGATCACTCTGTCCCGTCACTCTGCTATTTCACCTGNCAGNGAAATACCT GGTATCGTCCTGCCAACGTGAAGCATTGAATGCTTNATACGTCTCCATCCTGATTGTTTA GGCTTTGAATGCTGAGAAGTATCTGCACTTTGTTGGTCA

Sequence 736

TABLE 1 119/467

GTGNGGATTAACATAAATAAAATGATGCGCAAATGAACACAAAATTCAAATTGATGATGTGTACCTGCCC

Sequence 737

TNTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTCCCTGAGCAGTCGAAG
TGGATGCCCAGACCAATGGCCAGTGCTAATATCAATGCAANGATCCCAATGACGATGATT
GGAAAAAACTTCAATGGCAGCAGTGACAGGATCTGTGCAGCAACAGCATCTGCATCTGGT
GCAACAGGACTTATTTTCAAATCATCAAGGCCAAAAAGCGATCGGAATGAGAAGGGGGCT
TCAACAGCAGGCGGATCATTTTCCCCCATGGTGACTATTTCAGGACCTCTGACATCCGGC
TCCGCCTCCACCTCTACCTCATAATTCCCGAGTCCCAAAAATGTAGATGGCACCACGGAA
GAGATAGTAGGCCACAGTGTTACTGGCTTCCCATAAACACAGCCCTTTCCTGGCTCACAC
GGGGCATGACCTCCCGCGTACCT

Sequence 738

Sequence 741

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTACAGTATAAATCATGCT CCTGCTGTCTAGAGCTTACCACCCAACGAGGGCTTCAGATAAGATCAGCAACTGCCCTAG AGTGTGGAACTCCTATGACAAGGTGAGCCTGGGGTGTGATGGAAACACGGCGTGCATGGT TACCAAGCCACGCTTCCAGGGAAAGGGGTCCGTGCGGGAAAAACTTCAGAGAGGAAATGA CATGTCAGTCAATAACCTGAAAGAACTGGNTGAGAGTTAAGCANCAGGGAACAAGGGCAC AGTNNTCCACACAGCTTTTTGGAAAGATCATGTTGNTTATAGTGCAAAAAAATACTGAAT ATGGGAAACAATTTGTTATTATTTTTTAGGAGTNTTGCTTTGTCCCCCAGGCTGGAGTGC

Sequence 742

ACTACTATTGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTTGGGGGGAAAA AGAGTTACAATTTGCCCATAAAGAATGGAGAGAACAGAAATGTANCTTTTATGCTGAAAA ACAAAATGCAAGGGCAATCCAGTTTCTAATTCCTGTGCCAAAGCTGCTGTTCTTGATGAC CTCGGTCAAATCATTTAAATTCTCTCAATTTGTTCATATAAAAGTGCTATTAACCTGCAG TTCCTTCAAATACCAATCAATGTTGGCTACTTGATTTTCA Sequence 743

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTATTCACAGGGTATGCATAAA

TABLE 1 120/467

CCAAATATACAAGAATTTAATGACAGCATTATTTGCAAACAGTGAAAGATTCTGAGCAAT CAAAAGGTTCATTACTACAGGCATAGGTCTATAAATTACTACTGTATGGAATACTATGCA GCCATTAAAATAATGAGGAAGAGGGAGAGTGCCCTGTATGCACTGACATGGAAAGGTTTC AGTATATGGTAAAAAGCAGCTCATCTTAGAACAGATTTTATAGTATGACCCCACTTGTGT GGAAATATTTTGTGATGTGCCACTCAGTGTATACGTATTCATGAGTGCATATACAAGTGT GTGAGAAGCAATGTAAGTAACTGTTTCACAAGGACCCCCCCTTTAAGAAGGCAGAGGGGA TCGGGGGGATATAGAGTGAAGGGATGATTTTTGCTTTTTCCTCTA

CCGCGGTGGCGGCCGAGGTACGCGGGAGGAAAGGGCTGTGTTTATGGGAAGCCAGTAACA CTGTGGCCTACTATCTCTTCCGTGGTGCCATCTACATTTTTGGGACTCGGGAATTATGAG GTAGAGGTGGAGGCGGAGCCGGATGTNAGAGGTCCTGAAATAGTCACCATGGGGGAAAAT GATCCGCCTGCTGTTGAAGCCCCCTTCTCATTCCCGATCGCTTTTTGGCCTTGATGATTT GAAA

Sequence 745

Sequence 744

CCGGGCAGGTACACAGTAAGTGAAGGGCCAAGACTGACGGCTGATAGGACAGGGGTGACC
AGNGGTGGGGAGGGTAGTGGGAGCAGTCCATCCTGGAATCTGGCATTCAAGGGGCGCATT
GTCTGTGGGAGGATTTAAAAATAAAACCAACTAAAGGCAGTCTGCTTTTTATGGTCA
CCAGGCCGCCAGCAATTCTAAATTTCAGTGATAAAATATTCCTCCTCACTGGACACGAGA
AGCTGGCTTTCTCCTTATTCCCCAGTACCTTNGGCCCGCTTCTAGAAACTAGGTGGGATC
CCCCCCGGGGCTGCAGGGAATTTCCGATATTCAAAGCCTTATCCGAATACCCGTCGACCC
TTTNGANGGGGGGG

Sequence 746

Sequence 747

Sequence 748

GCCCGGCATGGTACCTGTGGGAAAAGAATGCTTGCAAAGCTTGTCACCCTCACGAGAA
TTCCTGTGACAGACATTTGCCTTTGACAGTGAAAACAGATATTAAAGTGAAAGGAGAAGA
AACCGAAGAGCATCAGAGGGGACGACTGGGTTACTTAACTGTTGGGGAGCAATCTGAGGA
GTTGGTTACCAGAGAAACTGGCGATGGCGATCCCGTGAGCAACATCTCTCAGACCCATTT
TAAAATGCCGGGGGATACTTAATCATGCTGAAAAACAGCAGAGCCCTTGAGGTTTTTGGA
CTACATGTTGCAGAAAGAAGAAGAAGAAGNAATTTNTACCTTNNCCNAAAAATAAAAATATNNNA
NNNNGGTACCTCGGGCCCGGTTTTNAACTAGTGGGATTNCCCCCGGGCTTGAAGGAATTC
GNTNTTCAAAGCCTTNTTCGATCCCCGTCCNANCCTCNANGGGGGGGGGC
Sequence 749

AGGTACTTTTTTTTTTTTTTTTTTTTTTGGNCTAACTGNNNGGAGTATTTCTTTTACCCAA GATAAGTAAAAGCTACAACTCTTAGTATAAATATGNGTCCAAGTGCCTNATAACTGCTAA CCACAGGGATCCTGAGCTCTNATAGCTTAAACACACAGNGTNNATTTTACTGGTCTACTT CTCCTGNAGACCTAAAAGGGCCTATAGCCTCAGTAGTTGACAAAACAACATATTAAAATT

TABLE 1 121/467

CCTCACTGATCACTAACATAACCTAAAATCCCTGCTTTTGACATTAGCATGGNANACATCCTTAGCAGGCCTAAATAGAATGGCCTTATAAGTGGATCCAAAGGGC

Sequence 750

Sequence 751

Sequence 752

Sequence 753

Sequence 754

Sequence 755

GCCGAGGTACANACAAGGGGGCNACTGNCATGGGGGNGGNNTCTGGTCTTGTAGTCNGTT TGGAATTTTCTAAGTCAGGGTGGGGTGGGGGGGACTGTGCACGGGTCATGTGCAGACTGGA ACCCATCTCCCCCTCGGTCTGCAAGTTAAAACAATTGGGTTGTCCTTCTCAGCATCTGCC AATGTCTCTTANTCAATCTTGGATCAAAAGGGCGTTGGAGGAGGGGGAAAT CCAGACAGTTCTCCGCCTCTGACATCAGGTCCAGCTGTTAGCATCGTGCTGTGGGTCCCT GAACAAGAAGCAAAGTCAGGACT

Sequence 756

AGGTACCGCTGTGTCCGGGTGGGTGGNGNGAATGCCGTGCTCCAGGTGTTCACAGCTGCT TCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTACGCAAATGTTGCCTGTGCC

TABLE 1 122/467

Sequence 758

Sequence 759

Sequence 760

Sequence 762

ATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGCGGGTGAAAAT GGAATAGTTTTCTAATTACAGAAAGAAAGAAGGGGGGNGTGGGNTTNTGCCATGTTGAGC ANGCTGGNCTCGAACTCCTGACCTCAGGNGATCAGCTCGCCTNAGCCTCCNAAAGTGCTG GGATTACAGGCATGAGCCACCACGCCTGGCCAAAAATNTTATNAATAATCCCCTTCTAAT

TABLE 1 123/467

TNCGGNCANCTTAATCACACACCAAATTCCTTTCATGAGATTAAACTNNCACAANTNCTA CACTTNCTTAAATNTTTGATNNTGNCCTATACTTNTTTTTTATATTNGCAATCTACTTT AGGACAGAAATTTACTTTCCTTTTCCTCTTGNTTTTGACCAANGTNCTNTCTTNTGCAAAA TGNANAATNNCTNTTTTTTCAACTTTCTTTACCAAAA

Sequence 763

TTAGGGCGATTGNAGCTCCCCGCGGTGGCGGCCGAGGTACATGTAATGCTCCTGAACTGT
ATGCTNGACACGGCTGTCTACNTAGGTTTTGTTCTGTGTATTTTATGACTATTTTTTAA
AAAGTAAACAAAAAAGAATTAGCTGGAAATACCAGCACAGGCAAACCCCTGGAGACAGAA
AGCAGGTGAGTGGTTGCTGGGGCTTGAGCAGGAGGAAGGGCGAGGGACTGCAGAATGGCC
ATGGGCTTTGCCTTCTAGCATGATGAGAATGTTCTGGAATTAGACAGTGGTAACGCTTGT
TCAACACTGCCAGTGTAGTTAATGTCACTGAATTATACACTTTAAATGGCTAACATGACC
AATTTTATGTTATATATATTTTACTACCACAAAAAAAACTAGCTGGCACCTAAAAAACATTC
CATT

Sequence 764

Sequence 765

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACGCGGGGGGTTCAAGCG
ATTCTCATGCCTCAGCCTCCCAAGTAGCTGGGACTAAAGGTATCCACCACCACGCCTGGC
TAATTTTTAGTAGAGATGGGGTTTCACCATGTTGATCAGGCTGGTCTCGAAC
TCCGGCCTCAAGTGATCTGCTCGCCTTGGCCTCCCAAAAGTGCTGGGATTACAGGCATGA
GCAGCTGTGCCCAGCTGGATAATTATTTAATAAATTGGGGAGCATAGGAAGCATAGTATT
TGTGAAGTGGGTAGGCAGGTGGATGGGGGGTAGGTGATGTTACATTTTGGAGGTTCTTCTGAGTTGAGCACCTTTATCTCA
TTTTAGCCAACAGACATTGAATACCTACCAAGTCTTAGGTATTTGCA

Sequence 767

GGCATGGCCTGAG

AGGTACACACAGTGATTTGGGGTCCTTTTTCCTAAAACAGCTTCTTTATCAGGACTTTGG
AATTCTGGGTGAGATAGAAACACTGAAAACAGGGCGGAAGTTTTTCTTCTGGCTTCTTA
GTCCATGGAGGGCTCAGCGTGGAGAGGATATGCCGTGGCATTCTCCCTGGGAGACCACAC
ATGTTCCCGACAGCTCAGACCCCAGACCCGCACATGCTTCTTGACAGTTNAAACCCCAAA
CCGNAGGNGCTCCCGACAGNTNAAACCCCANACCCCGCGTACCTGCCCG
Sequence 768

Sequence 769

TABLE 1 124/467

TAACTCAGATGGAAATGCAGAAATCACCCGTCTTCTGCGTCGCTCACGCTGGGAGCTGTA GACCGGAGCTTGTTCTAATTNGGCNATTTGGGTTCNTCCCCCCGGGNNCNTN Sequence 770

Sequence 771

Sequence 772

Sequence 773

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCACCCTGCTGAGGG ACATCCAGGACAAGGTCACCACACTCTACAAAGGCAGTCAACTACATGACACATTTCGCT TCTGCCTGGTCACCAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCT CCTCCAATTTGGACCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCT CATTCCATTGGCTGGGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGT CATCAGTTTATCAACCAACAAGCAG

Sequence 774

CCGCGGTGGCGCCCCGGGCAGGTACACTACTGGCATAAGAGTAAATTGGTGAGAACT
TTCTGGAGGGGTAGTTTGGCAATGTGTTTCCAAAAAATCTAAAAATTATATTTGCCTCTA
ATCCAGCAATTATACCTCTAGAAATTAATACTAAGGAAAATCTTAAGAATATACCGTAAA
ACTTTAGTTGTAAGAAATTTTTTTGTGGCCAGGCATGGTGGCTCACACCTGTAATCCCAG
ACTTTGGGAGACCAAGGTGGGCGGATCTCCTGACCTCATGATCCACCCGCCTCGACCTCC
CAAAGTGCTGGGATTACAGGCGTGAGCAAATTTTAAATAAGAAGAAAACAGTCAACAGCAT
CAGACATAGTAGGTATGTCCAACACCATAATGGCTGAAAAGTGCCCCCTAGTCTGGCAAT

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TAGTAGGTCATTGGTTTATTAATAACCGGCATGTTAAAGTTG

Sequence 776

Sequence 777

Sequence 779

CACTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTATGAGAATTTCA
AACAAAGAATGAAGCCATAAAACAAAAAGACTGAATATTTGGCTCTGCCTGGCTCCCAGG
CTTTCTACTATTCTTGTGACTTGGCCTCAACAAAATCTAAAGTGACTTGTTATTTGTGGG
TCAGCTTTGTCCCATCCTTACCAGTCATGGCTTTAGACAAAAGACTCAGCACCACTCACC
CTCTGGGACAGTCTGACTGTGGTCTGAGGCCCCTTGCTTAGATATTAGGCTTCAGCTCAG
TTCC

Sequence 780

Sequence 782

Sequence 783

CNATTGAGCTCCCGCGGTGGCGGCCGAGGNCTGATGTCCTACAGTCCTCACCTGATCT ACGTTCACTGGAAAGTGTNGAGTCTCAGCAGGAAGCACCTTGCTCTCGTGTCCGGCTAAT

TABLE 1 126/467

TCGAGTGCTTTACGTAAGTAGAGGAATTGCTGACTTTTGGGACATTTCTGGTCTTGCCAA AGTTCACCTTGTAGTAAAGCCCCCAAAGATACTTCCCAAATAGATGCTCTCTTGAAAATA ACTCAG

Sequence 784

Sequence 785

GCTCCCGCGGTGGCGGCCGGCAGGTACGAAATGAGAGAAATGGTTTAGTAAACGTATAA GACATCAACATAGNAAAGTATTCTATAGGNNTATGTGTTGGAATTACAAAGATGAAGAAA AGATACAGGCAAGTATTTGATATACTNAATTAAAAATAGCAAGATGTAGAGTAGNCATGT ATACAGTGATAGCAAGAACATGGATCCTTAAGGACAAAACTGAAACATAATGCAAAAAAA GAAAAATATGCAAATTATTTTTCGTATGATGTAAGTTGTAAATAT

Sequence 786

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGNGTACNCGGGCCTATTTCTGAA
TAACTCAGNGGCTTAAAATTATATCCCAAAGTAGNGGTATCACAGGGTTTCCTGATGAGG
ATAAATGGGCCTGAAGTGCTTATGGGCACCCACTATGTATCATGGNAAAACTTGCACGTG
TGTGTGTGTTGAGAGAGAGAGAAAAAANAATAGANAAAGTTGGTGAGAAAAAGGGNAGG
CTGTTTTTTGNNCCGAGGGNTGTNTGGTTGGGCTTT

Sequence 787

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGNACACANTAAGTGAAGGGCC
AAGACTGACGGCTGATAGGACAGGGGTGACCAGTGGTGGGAGGGTAGTGGGAGCAGTCC
ATCCTGGAATCTGGCATTCAAGGGGCGCATTGTCTGTGGAGGATTTAAAAATAATAAAAC
CAACTAAAGGCAGTCTGCTTTTTATGGTCACCAGGCGCCAGCAATTCTAAATTTCAGTGA
TAAAATATTCCTCCTCACTGGACACGAGAAGCTGGCTTNTCCTATTCCCCAGTACCTGCC
CG

Sequence 788

GGNGGCGGCCGCCGGTTTTGGACGCGGGTNTNTGCCCTNACTTTTTTTAGCGGAGCAGAG GAAACATTCATAAGGAAATATGCGAGTAGAGCTCAGGAGAAAAGCAGGACTAGAGGCCCA AGAATCACAGGCCAGAAGAAGAAGCTGTAGCCTCGGGAATGGAAGAGCTCTCTGAAGGGG AAAGGGGAGAACAGGAATGTNCCAGGAGCCAAGGCTCATCTATAAGGGACTTNCACATTT AGGATGTAGAAGAAGGAAGCAGAGCAGGGGATGACCAGAAATGGCCCCAGAGATGAGAT GAAAGTTAGGAGAGCGGNGAGCAAGCCTTTAGGTTTCACAAGGGAAGGAGGGAAAGTAGG TGTTAGGTGCTGCCAAGATCAGGGAAAATAAGCAGAAGACCAGGCCATTTTNANTTGCNG TGG

Sequence 789

CCGCGGTGGCGCCGAGGTACCACAATCAACTCAATCACAACATATTACAACAAAACCCT
TCATCTTTTTCCTTAACCCACTGTAACACAAAGCAGAGAATACAGATTAGCTTTTTTATT
TGTCTGTTTGACTTCATCTCTTACATACCTCTATTTCAGTATCTATGATATTTTCCTCTT
CTTATCTGTTCAATGACAGTCTTCCCTTTTAATATTCTAAACTTGTCAAGCACAGCANTT
AAAAAAGTATTCTCATGTATATATTTTATCTTTAGAGCATCGCATAAAGNCTGATACATA
GGAAGTTTTAGATGCATATTTTACATTGGGTAGATCCAGGGGAAAAG
Sequence 790

CCGCGGTGGCGCCCGGGCAGGTACTGCCCAAGAGAGACGTCTCTTACTGCCTCATT
AAGCATTTGGAGCTGTTAAACACAAATCAAGGCAACCAGAAAGGGCATCTTGGCTTCAGG

TABLE 1 127/467

CTGGGCATAACCATCCCATTTGCCACATAAAAGTCTAGTGGCTACTCTGCACCCTTTCTG GGTAGAAGCAGAGTTAGTTTGGTCATGGGGGCCCCTGTGGGACAGTGTTGCCCAGACAGG TACCTCGGCCGCTCTAGAACTAG

Sequence 791

Sequence 792

Sequence 793

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGCAGGTACCAAGTATACCTTTT
CATTTAAATCATTGAACAGTTCACAATGGCTGTTGTAAAGTTTTTGCCTTGTTACTGAAA
CCATCATCTCTTGGTCTATTTCTATGGAGTTATTTTTCCTAGTTATTGGCAGTTTGCTT
ATCTTTTATGTGTCTAATAACTTTTAATTGAATGTAGAACATTATGGATCTTATATTTTT
GAGAATCTGAATGTTTAAAATTCCTTTGAAGAGTTTGTGTTTTCTTCTGGAGGCAGTTTA
CTTACTGGCTGTGAGCTCAGTCCTGTTGAGGCTGTTTNGCGACNNNCTGTGGCTTTGTCA
GGGTGGGGTGGTGGATCAGACATCTGGTCATCAAC

Sequence 794

Sequence 795

Sequence 796

CCCCCCGGAGTTTCAGCGAAAANCCCGGCCGAGGNACCNCNCCNTTACNCCCAGGNTT ANAAACNCCCNGGTNTNGNCCCAGGAGAGGCGGGGGANCACCGCGCCNGGCCAGCANGGN

TABLE 1 128/467

Sequence 798

CGGTGCCGCCCGGGCTTGGTACCCTCTGTCACGGCTTCCCTTTGCTGAAAAGGGA ATTTCCCAACCCCGGGTGAGGCAATGCCCCGCCCTGCTCCGTGGGCTGCACCTGCTGTCT GTCAAGCCCCAATGAGATGAACCCTGTACGCGGGGGCCTGGGATCTCAAAATGGCGGCCC CGTGCGGAAACAGCGTNTGGGAGCAGANATTGTTGCCTCCTGAA Sequence 800

GGGCGNTTTGGAGCTCCCCNCGGTGGCGGCCGGGCAGGTACTATCTGGAACNTGTAGCTT CCTTTNGCACTGCAGCATGGGAAGCCAGAGTTGATGATTCATACACCAGCATTTACATTT TTCAGCATGAAAGTGGTATGTTCTTCAACTCACAACCCATTGGCCAGAACCAGTAACATG ACTTCACCTAACTGCAAACTAGCTGGAGAATTGTGGGAGAGCTCATGG Sequence 801

Sequence 802

TABLE 1 129/467

Sequence 803

AACGACCGCCCGGGCAGGTACTAAGCCAGGACCTCAGTTAGCACTAAGCACTCTTACTAT
TGCCCCCACCTGGCACAAAGCAAACTGAGATCTTAGTTGGGCCCATCATGTGTCATCTGA
TTGTCTTAGAAGTTCTTTTTTTTCTAAGACAGAGTTTTGCTCTTTTTGGCTCAGGCTGGAGT
CCAATGGCACAATCTCGGCTTACTGCAACCTCCGCCTCCCAGGTTAAAAGCGATCCTCCC
GCCTCAGCCCTNCGAGTAGCCGGGACCACAGGCACCCGCCACCACGCCCGGNTAACCTT
Sequence 804

Sequence 805

CCGGGCAGGTACAATGGACTTTGACAGTTCTTCCCAAACAGATCCTAATTTTAAACATTA
GGTTTGCTTTGATTCTTTCCTTGGGGCTAAGAGCTCACAAAGACTTAGGTTCTGGTCAT
GGCTCCAGAGGCCACACATTCCAGGACAAAGTCTCTCTACAGTCAACGCCTTAGTCCCAC
ATCTGTAAAATCGGAATAATCATCCCTGATCCAGCTATCACATTGCAGTAGAGTGAGACT
CAAATGAGATAATGGAAGACAGTGGGAATGATCATTTCCAACTTGGCCTGGCTGACCCAT
TCCTTGTTCTAAAGTCAGCTCAGGTTTCACCTCTTCCAGNGAAGTTGACCTGGCACTTTC
TTTTAGGATGGCTACTGCTCCTCTGGGTGCCCCGGGGCTCANTGTCTCCCCATCACCGCC
CATGGCACACTTGGAGTGACTGGTCCTTTACTTTGNTT

Sequence 806

TNCGGGCAAGGTACATTGGCCCCAAAGAGNAGGAATTCCTTGTAGAGGAGCTTGTAGATG CTTNCCCTCCAGCGGAGAAGCAGGCCAGAGAAACCTCCGAAGCGGGCCTCCGCCACTTTG AGAGTGTATGAAACCGTCATGGTGCTGGGAGCCTGGGGCAGGAGGTCACAAGAGTTGCCC CCAGGGCTGTCGTTTAGTTCTCCAGACAACCTCCCTTCCACTCTGGTCTCACACACCCCA GCCTTCACCCTGCGTCAGTGGACAAGGGGGTAGGAGCCTGCAGAGCAGAAAAGTACCT Sequence 807

Sequence 808

CCGCGGTGGCGGCCGAGGTACGAGACTTGTCACCATGTGACATGGCAGCTTCAGAAACTT
AGCCACTGCCAAAAAAAAGAGCAGGCAGGGATAATGTTGTCCCATTGTCCAGTCAGAGAGA
CCTGTTGAGTCTCTAGTTTGCCAGTCCCCAAGAGACCTTTGGAGTTTTGCTGGAGCCAGA
CATCCTGCTTAGAGATGAGGAAGATCCTGCTGTTCCGTGGGGAGCTCTTGAGACACCCGT
GCCACCACCCACCTTCTCCTGATTGCCACTTGCTGCCCTTTTCCCATTACCCTCTCTGA
CTCCATAAACATCTTCAAGTCTTCCCTTTCTCCACCCCAAAAAATGCCCACCTTGGAAAG

Sequence 809

AAATTAATTGGGGTTGNGCTAACTGCCCGGTTTTCAATCNNGNAAACCTTGTGGGGCCCA NNTGAATTAANANAATNGGNCCACCCCCCGGGGAAAAGGGNGGTTTTNNAANTTTTGGG GCCTTTTTCCCCTTTTTTAAAAAA

Sequence 810

TABLE 1 130/467

CCGCGGTGGCGCCCCGGNCACGGTACGCGGGGATGTCTTCTGAGAGAGTCAGGGCAG CTGAAGACTGGGTGAGGGTGAGGGAAGCCGCTGGTGTCCTCCTCAGTCACCCGTGAGAGG ACTCCTNTGTGGAGCTAATCAACTGCAAGGAAGATTGTTCCCAGTGTCCAGACCTGAAGG AGTCTGGACCCATAGTGCANTGAGATTTGGGGAAGGAAGGATTCCGGATAGGGGTGAGCT TTNTGNTGATAAGCAAATGTGAAC

Sequence 811

CCGCGGTGGCGCCCCGGGCAGGTACGCGGGGGTGTTTATGGGAAGCCAGTAACACTG TGGCCTACTATCTCTCCGTGGTGCCATCTACATTTTTGGGACTCGGGAATTATGAGGTA GAGGTGGAGGCGGAGCCGGATGTCAGAGGTCCTGAAATAGTCACCATGGGGGAAAATGAT CCGCCTGCTGTTGAAGCCCCCTTNTNATTCCGATCGCTTTTTGGCCTTGATGATTTGAAA ATA

Sequence 812

Sequence 814

CCGCGGTGGCGGCCGAGGTACATTATTCATATCCAGCACTCCCTGCGGCTGCTGCTGAG
GAGCAGTTATCCAACAAGGACTGTTTCAACCTCATCGCGTTTGGAAGCACAATTGAAAGC
TGGAGGCCTGAGATGGTTCCCGTGAGTCACAACAATTTACAAAGTGCCTGGCGGTAGGTT
ATGGGCAGAGACTTCGTGGGGCTGTGTCTGAGGGAAGGTTTGCAGGCATTGTTTTCTCTG
TCCCCCTCTCCACCAAGAAGTAGCTCTCTAGAGTCCCTGACCCCAAACAGCCATGGGCAG
AAATCAGAAAACAGCTTCCTTCTGTCTGCTGCTCCCCCACCTGGCCATCTTCACTTTAT
GAGAGTAATGACATCGACTCCATCACGTCTGAGATGGGAAAAAAGGCTCTTCAGCTACTCC
CAAAAGGGTATGCCCTGGGCATGGG

Sequence 815

Sequence 816

TABLE 1 131/467

GGATGGCGGCTTCATTTTTGTCCCTCCTACCTCTGA

Seguence 817

GAACCTAGGGCGATTTGGAGCTACCCNCGGTGGCGGCCGAGGTACATTTTGGCAAACCGT GAAGGGCTTTCNTTTTNGCAGGTTGGACTTCCCCCCCCTAGTNGGCAGGATTTTTTTTTAG GGGACCACCTGAGAAAGGTCTGTTACCGTGCATAAACCTCCTTTAACACCTTTTAAAAAC TCTTCTGGGGGCCGGACTCAGTGGCTCATGCCTGTAATCCCACCACTTTGGGAGGCTGAG GCAGATGGATCACCTGAAGTCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCCC GTCTCTACTAAAAATAGAAAAATTAGCCAGGAGTGGTGGCAGGTCCCTGTAATCCCAACT ACTTGGGAGGCTGAGGCAGGAGAATTGCTTGAACCCAGGAGGC

Sequence 818

GCCAGGAAACCCGTAAAAAGGGCCCNGTTTGTTGGCGGTTTTTTTCCATAAGGGTTTCCG CCCCCCTTGACCGAGGCANTTAACAAAAAATNGACNGCTTCAANGTCAGAAGGTGGGC Sequence 819

Sequence 820

TAGGGCGNTTTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCACCCTGCTGAGGGACAT CCAGGNCAAGGTCACCACACTCTACAAAGGCAGTCAACTACATGACGCATTCCGCTTCTG TCTGGTCACCAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTC CAATTTGGACCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATT CCATTGGCTGGGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATC AGTTTATCAACCAACAAGCAGTTCCAGCACCCAGCACTTTTTACCTGAATTTTAC Sequence 821

Sequence 822

CCGGCAGGTACGCGGGAGGTCATGCCCGTGTGAGCCAGGAAAGGGCTGTGTTTATGGGA
AGCCAGTAACACTGTGGCCTACTATCTCTCCGTGGTGCCATCTACATTTTTGGGACTCG
GGAATTATGAGGTAGAGGTGGAGGCGGAGCCGGATGTCAGAGGTCCTGAAATAGTCACCA
TGGGGGAAAATGATCCGCCTGCTGTTGAAGCCCCCTTCTCATTCCGATCGCTTTTTTGGCC
TTGATGATTTGAAAATAAGTCCTGTTGCACCANATGCAGATGCTGNTGCTGCACAGANCC
TGTCACTGCTGCCATTGAAGTTTTTTTCCAATCATCGTCATTGGGATCATTGCATTGATA
TTAGCACTGGCCATTGGTCTGGGCATNCACTTTCGACTGCTCAGGGAAGTACCTCGGCCG
CT

Sequence 823

ACACTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGTGTT
AGCTATTATCATCACCCTCCTTGCTAGGCAGAGCAGGACAGTGGGGAATTGATGTTTCCT
CCCCTCCATCTCACAGGTGGGGCAGGGGTGTGCTGAGAAGAGAACTTGGGACTCTTGGCC
CCTGTTCAATTCTCTGCTTAACCTGCTAGGCAATTTGGGCCTCTGAAAATTCAGTAATCC
TCATAGCAACTTAGACGTCACCTGGGCCTGTGGTCCCCTTCCTAGCCTAGGAGTCAGAGC
ATGAAGCTCCATCTGTCACATTGGTTTGTTCAGAGAACTACACATGCGTTTTATTTTAGC

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AGCATACAGGTTCCCACTTAGGCATTGAGAGGACATAGGAAGCTGTTTAACTTCCTA
Sequence 824

Sequence 825

CCGCGGTGGCGGCCGAGGTACAGATGTATGGATCTCATAGCATTGAGGGGTCTTTCAGAT
TATGTTTCAAACCCCTCACTTTCTCTTTTCAGATAAGACCACAGCGACCTGGGAAAGTG
CAACGTCTTAGCCAAAGACACAGAACTATTTAGCGACACTGTCTAGACTCTAGTTTCCAT
GTCTCCTGACTTCAGTCTAGTGTTCCACCCCTGCCGCCCACCCCTGCCCCATCCTCATTC
CTCCTGTAGGAGAGGCCAGACCTTTGCCTGCTGCAGCTTGTGGCTCTTCTCCTGCCTTCA
GTTNTTCCATTGCCTG

Sequence 826

GGGNNAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGCAGGTACCTGTCTGGGCAACACT GTCCCGNNGGGGCCCCCATGACCAAACTAACTCTGCTTCTACCCAGAAAGGGTGCAGAGT GGCCACTAGACTTTTATGTGGCAAATGGGATGGTTATGCCCAGCCTGAAGCCAAGATGCC CTTTCTGGTTGCCTTGATTTGTGTTTAACAGCTCCAAATGCTTAATGAGGCAGTAAGAGA CGTCTCTCTTGGGCAGTACCT

Sequence 827

Sequence 828

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCACCCTGCTGAGGGACA
TCCAGGACAAGGTCACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCT
GCCTGGTCACCAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCT
CCAATTTGGACCCCAGCCTGGTGGAGCANGTCTTTCNAGATANGACCCTGAATGCCTNAT
TCCATTGGGCTGGGGCTTCCACCTACCAAGTTGGGTGGGACATCCATGTGACAGAAATGG
AGTCATCAGTTTATCAACCAACAAGCAGCTCCAGCACCCAGCACTTNTACCTGAATTTTA
CCATCACCAACCTACCATATTCCCAGGACAAAGCCCAGCCCGGCCCCCCC

Sequence 829

CGAATTGGAGCTCCCCGCGGNGGCGGCCGAGGTACCTGATCTACTCCTCTCTACAACAAC CTTGTGGGTGACGTTATTATCTCCATTTCACAAATGAGGCCACAGAGGTTCTAAAGGGTA AATGACGATGATGATGAGAGGTAAAGTGATAAAACAATGTCTCCTGACCACAAATCCTGGA ATTTAAACATAAGNGTAGTAAACATGAACTCTAGGAAGCCTCCTGGGGCTTCTNCCTGTG TCTGGAGCCCCTGCACATGCCCAAAGGAAGTCCTTTTGGTTCTNCGNTCAGNAGAGAAAG GGNGCATTTCACTAAAAGGGAGGTGGGGAAACAAGACTGGTGGTAGGG

Sequence 830

CCGCGGTGGCGGCCGAGGTACATTATTCATATCCAGCACTCCCTGCGGCTGCTGGAGGAGCAGTTATCCAACAAGGACTGTTTCAACCTCATCGCGTTTTGAAAGCACAATTGAAAGC

TABLE 1 133/467

TGGAGGCCTGAGATGGTTCCCGTGAGTCACAACAATTTACAAAGTGCCTGGCGGTAGGTT
ATGGGCAGAGACTTCGTGGGGGCTGTGTCTGAGGGAAGGTTTGCAGGCATTGTTTTCTCTG
TCCCCTCTCCACCAAGAAGTAGCTCTCTAGAGTCCCTGACCCCAAACAGCCATGGGCAG
AAATCAGAAAACAGCTTCCTTCTGTCTGCTGCTCTCCCCACCTGGCCATCTTCACTTTAT
GAGAGTAATGACATCGACTCCATTCACGTCTGAGATGGAAAAGGCTCTCAGCTACTCCCA
AAAGGTATGCCCTGGGCATGG

Sequence 831

CCGCGGTGGCGGCCGAGGTACGCGGGTAACAGGAGTCTTTGCTGAGTGATCATCTGTTTA
TTCTTTTACTCCACAAATATCGAATGTTTACAGCGTGCCTGGCACTGAGCAGGGCTGGGG
TTTCCTGACCATATGGACCTTCCTGGGTATATCTGTGGGGCTTGAATGGTGTGACCTT
GTGTCCTGCCCG

Sequence 832

CGGGCAGGTNCGCGGGGGTGTTTATGGGAAGCCAGTAACACTGTGGCCTACTATCTCTTC CGTGGTGCCATCTACATTTTTGGGACTCGGGAATTATGAGGTAGAGGTGGAGGCGGAGCC GGATGTCAGAGGTCCTGAAATAGTCACCATGGGGGAAAATGATCCGCCTGCTGTTGAAGC CCCCTTCTCATTCCGATCGCTTTTTTGGCCTTGATGATTTTGAAAATAAGTCCTGTTGCACC AGATGCAGATGCTGTTGCACAGATCCTGTCACTGCCATTGAAAGTTTTTTNCA ATCATCGNCATTGGGATCATTGCATTGGATATTAACCCCTGGNCAATNGGCTTGGGCATT CAATTTGACTTGNTAAGGGAAGTNCCTCGGCCGNTNTANAACTAGNGGGATCCCCCGGCT GGANGAATTTCAATTTNAACTTATTGATACCGTCCANCCTTGNGGGGGG

ACCGCNGTGGCGGCCGGGCAGGTACATCACCCTGCTGAGGGACTTTTNNGGACAAG GTCACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTCACC AACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTGGAC CCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTGGCTG GGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATCAGTTTTATCA AC

Sequence 834

Sequence 833

Sequence 835

Sequence 836

GNGGNGCCGCCGAGGTACTTTAACANGCCATACTCCAGTCCCAACAATGTTAAATGCCA
AAGCAGTGTTGGTAAAAGCCTCAAATGGTGAAAAGGACAGAAACTCAAACCCGCCCTTGT
GCCAGTAAGTAACTGTTACTTATCTCACAAAGCGCTTGGCTCTGGAAACAATCTAACTCT
GAGCTGCACGTGGAGTCTACATGGGAATGTGCAAAGCATGTATTTCCTTTTAGGTGCAGC
AGAGGTAACCGAAATTCAGATAAGAGAAAAAAAATCCAGATTTCAATGCAAGAGGTGGAA

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Sequence 837

NTTGCGTTGCGCTNACTGNCCCGCTTTCCAGTNCGGNGTAAACCTGTCGTGCCCAGCCTG CATTAATGAAATCGGCNCAACGCGCGGGTGAGAGGCCGGTTTGCGTATTTGGGCCGCTCT TCCCGCTTTCTTCGCTCACCTGACTCCGCTGCGCCTCGGGTCGT

Sequence 838

Sequence 839

Sequence 841

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CCGGA

Sequence 843

Sequence 844

CCGCGGTGGCGGCGAGGTACGCGGGGAGGTCATGCCCGTGTGAGCCAGGAAAGGGCTGT GTTTATGGGAAGCCAGTAACACTGTGGCCTACTATCTCTTCCGNGGTGCCATCTACATTT TTGGGACTCGGGAATTATGAGGTAGAGGTGGAGGCGGAGCCGGATGTCAGAGGTCCTGAA NTAGTCACCATGGGGGAAAATGATCCGCCTGCTGTTGAAGCCCCCTTCTCATTCCGATCG CTTTTTGGCCTTGATGATTTGAAAATAAGTCCTGTTGCACCAGATGCANATGCTGTTGCT GCACAGATCCTGTCACTGCCATTGAA

Sequence 845

Sequence 846

Sequence 847

TGGAGCTCNCCGCGGTGGCGGCCGNGGTACTCCAAGCAGTCCCAAAGTGGGAGTNCTTAA AACACCATGGGCAGGTGAATGGCTGACCAGGTGGAGGTGCACCAGTGCACCATGACAAGAG CAGTGGAAAATGGGTGAATCTGAGATGCCTGGAGGCGAGGGGGAAAGAGCACCATCACAGA GGACAACGTCCANNGGGACACCCTTTTATA

Sequence 848

CCGCGGTGGCGCTGTGGACTGAAGGGTGACTGGTTCCACTGTGGTCTCCATGGGAACAA GTTGTTTCTGGAGTCTTCCAAGGAGAATTTCTCACAGTGGACCTGATCTCTGGGCTGATG CTGGGTTCCTTGGAGCTCATGATTTTGAGAGTGGTAGACATTTCTGGGCTTCCTGGGGAT GTGCCTGCTGGACTGCTCCCCGTCTCCTCTGCTGGGGCAGGCCACGTGGAATTTCCTTGT GCTGCCTGGCTTGACATCTTTA

Sequence 849

TABLE 1 136/467

CAAGCTTTTTN

Sequence 850

CCGGGCAGGTACATGAAAGTAAGATCACAACCACAGGAACCACACAAAATTCAAGGCACC
AGAGGAGCCCAGACTTGGCTGGCAATGCCTGTTTTGGAGCTATTCCACATTTCTGGAAGT
CAATGGGAATACCGGAATATGAAAACACTATGAGGCCGGGCACAGTGGCTCACGCCTGTA
ATCCCAGCACTTTGGGAGGCCGAGGCGGGCGGATCATGAGGTCAGGAGTTCGAGACTAGC
CTGGCCAACATAGTGAAACCCCATCTTTAATAAAAAATACAAAAAATTAGCCGGGCGTGGT
GGGGGGTGCCTGTAATCCCAGCTACTCCGGCGGCTGAGGCAGGAGAATTGCTTGTACCTC
GGC

Sequence 851

Sequence 852

CNANAGGGCTTTTTGGGGGCAAAACCGCGGNGGCGGCCGCNCNAGAACNAGNGGANCCCT NTTGGGGGGGAAAAAAACCCCAAGCCCACCGANACCGNCGACCNCGAGGGGGGTNCCGG NACCCAGNGNNNGNCCCCTAAANAGAGGGNNAANNGCGCGCNNGGCGNAANCANGGNCAN AGCNNGNNNCCNGNGNGAAANNGNANCCGCNCACAATTTNTCTTTTNTAGNCGAGCCGGG AGCAGAAAGCCCNAAGAAAAAAGN

Sequence 853

AGGTACCCACAGCCCTTTCTTTTGGAATTCCCTAGAAGGGGTCTGTGCCACATACAGGAA
GTAGGAGGGTGTCTTTGCAGCATATTTCTTCTCTTTGGAGTTAACTGCGAACGTTGCACG
GCGACCTCTTGATCCATTCTGTGAAAGCCCCAAGCCTGTCATGCAATAAAGACGTCCAGT
TTCACCGCAGCAGGAGGCCGCATGAAATATTCCACTTGAACAAAACCACTTAGCAGTTT
ACATCAATGCTTACCCTGTCGCATTGAAAGTGATGTGAACCCACACCCAAGAGCCCCCAA
ACCAGCACGTTGATACCAAGTTTCCCCAGCTGCATCCAAATCAATTCCTTCTT
Sequence 854

Sequence 856

GCCAGGATTCAAACCAGGGANTTTGCTCCAGCACTCCGGCTCTTAACCTCAACCGTCTGC CTCTCCACAAACACCAGGATCAACCACCAAGACCAAAAAAACAGTCTCACAAACCATCAA ACATTGCACTTGGTGGCTCAGGACCTTAGCTTCGTCTTAAAGGTCCCTGTTATGCTTTTT CTTTTTGCCCCAGTGTGGAGTGGTCTTCGTGTTTGTGAGTGCAGGGGTCAGGGGTTGTGT CTTTTCTTCTTGTNCCCTTCCAAGAGGTGACATGTATCCTTGATACTGGAAGGGCCCTT Sequence 857

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Sequence 858

Sequence 859

Sequence 861

Sequence 862

Sequence 863

NCTATAGGGCNAATTGNAGCTCCCGCGGTGGCGGCCGAGGACAAATTCAGTCCCAATAC TCAATACGTATTATAGATGACTACGCGAAACCTTAGGATGNGATTNTCTGAATAATN GNTCTTTGTAGGATTTGGTTACATTATTTAAAATGAAAAAGATCTAGTTTTAGTGTGAGC TCAGTAATGNTAATNGGTTAAGTTCATTGCGAATCTTGAGTTTTAGATAAGTAGTTATTT TTTTCAATATCACTTCTGTTTTTAGTGATATTATATCAAGAAACAACGTATTCAAGAACC ATGGCTGACAGTGCCAGATATACTTAGGGGATAAACATCAAAATGCAATTATAGTTGCTAT AACGTTAGATACTCGGAATCAAAATTTATTTGCANGCTGACTTGATAAACTAAATGAA Sequence 864

TABLE 1 138/467

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACAAGAGTCAGCAG
AAATGTGTGCTTTAAGCAGAGTCACAGGGGCCTGGGGCTGAACTGAGTCATTTCTCAAAG
ATATCCCTGCCTGGGATGATGATGGCTCTAATTGAAGCTCTGGCATCATCTGGGGCTTTA
TGAGCCAAGGAGATAAGAAGAGCCACAGCAAAACCCTTGGGTCTACAGTGCAGGCTGCA
ACCAAGGCAGCATTTGCTAGAATATTTGTGATTATGTGTTCAACCTACAACCT
Sequence 865

Sequence 866

Sequence 867

Sequence 868

CTATAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGCCCGGGCAGGTACAGGATATCAC
CTGAATTATTAATGAATGCCCAGGAAGTAATTTTCTTCTCATTCTTCTAAAACTACTGCC
TTTCAAAGNGCACACACCGCGTNCACATACACTGCATTCGTTGCTCCAGTATAAATTA
CATGCATGAGCACCTTTCTGGCTTTTAAGCCAATATAATGGGCTGCAAAATGAAGACACC
ANAGTGTATGCATACAAATCTCACTGTATTAAAGATGCAGGTTTTCTAATTGTACCT
Sequence 869

Sequence 870

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Sequence 872

Sequence 873

Sequence 874

ACTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAAGACTTTGTAA
ATGTGATTCAGGGCCCCCAGCACCCCTGTGTCTGCAGAGTGCCTTCAAAACTCAGCTGTT
CCGGCCGGTGCCAACCTGTGAACTTCCCACCATATCCCAGAATCTGCTATTCCCCAAACC
ACTTCCCAGTTTCCTTTCAGTAATCTTTCTGAAGGAGCCAGGACAATAGGGCCTGTTGTT
TAGTGAATTTCTTTATTATTTTCAGCCTTTAAAATGTAATTTCCATCTCTTTGCAATGAAT
TTGTTTCCCTTTTTTTTTGCTTCATTTTGTTTAAATTTTCAGGTATTTTAGCTCCCCTTTCA
TATTATTTTTAAATTTTTTAATTACCTGTTGTAGGGGGTGTTCCTCCAGAAGCAAAGAGCA
AAATTTTACTGTTGTGTACCT

Sequence 876

CTACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGCAGGACGCGGGATTGA
TCAAAAGCTTTGTAACCACAGGAAAAAATAAACTCTTCCATCCCTTAAAGAATAGAATAG
TTTGTCCCTCTCATGGGAATTGGGCTGTATGTATATTGTTCTTCCTCCTTAGAATTTAGA
GATACAAGAGTTCTACTTAGAACTTTTCATGGACACAATTTCCACAACCTTTCAGATGCT
GATGTAGAGCTATTGGGAAAGAACTTCCAAACTCAGGAAGTTTGCAGAGAGCAGACAGCT
AGAGATAACTCGGGA

Sequence 877

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Sequence 878

Sequence 879

Sequence 880

CNCTACTATAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAATGGCGCAATCT CAGCTCACTGCAACCTCCACCTCCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCTGAG TAGCTGGGATTGCAGGCATGTGCCACCATGCTCGGCTAATTTTTTGTATTTTTAGTAGAA ACGGGGTTTCGCCATGTTGGCCAGCTGGTCTCCAACTCCTAACCTCAGGTGATCCACCCG CCTCGGCCTCCCAAAATGCATCTCTGGTCTTTAAATGCCCTTTGCTGTATATTCTATAAC ATCAAGTCTCAGATCTGGTTTGACCTCAGTTGGCCTCTTAATAGTTTTCCCCTATGAACA TTCTGGTCTCCCAGTAAGCCTGTAAGCAGCTGAGACCATCTCTTATATCCCA CATCGTCCCATG

Sequence 881

Sequence 882

Sequence 883

CCGCGGTGGCGGCCGGCCGGGCAGGTACTATAATTATAATGATTTCAGATAGAACATGCA

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ATTAGCCTTTTGAAATCCAACTTCTGTGCAAAATTTTAGTATCAGAAAATACGAGATTTG
CAGGGGGAAACATCAGTAAACTACCATTAATGTCAATGCCCAGTTTTGACTTTTGTTAGC
CTGACACTCCCAAACAGTTGTAGAATCCGATAGATGACTGATGGCAAAAGATTGTGAACA
TGTGGAAGAAAATCAGTGGGATTCGGTGCTGATGAATAGGTTGCCTTCAGAGTATTATTG
ACAGACAGCTTGTGGAACTAATTCTTTATTTTTGATGTTGTGGGAATTAACACATCAATG
GTGGTTATGGGAACTACCAATGGGTTCCTACAAT

Sequence 884

Sequence 885

Sequence 886

Sequence 889

TABLE 1 142/467

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCTGGATCTATGCTGC
TATGGGTGAGAATCGACATCCTTTGAAACTGGCCACAGGCAGAGCTAAGAGGATGACTA
AAAGGTCCCTTGGGTGGTGCTAATGAGCAGGGGCCCAGGAAAACCTCTGTCTTCCCGGA
GAGCCCTCTTGCATGAGTTTCGGCTTTGCCAAGATTCCAGGGACTTGAGGACAGCTATTG
AGTTATGGTTACGTGACTGCCACATTGGGGCTTGGAGGCATCTGGCAGATGGTTGGGAAT
GGGCTGGCACCACACTAATTAGGCCACGATGATCCAGTTTGACTCAGGGAAACCCAGAAG
TCATAGTNCTCTTTGCAGAATGACACAAGGATGTCAACATGCTTTGNTTGTGTACCTCGG
CCCGCTCTAGAACTAAGTGGGATCC

Sequence 890

Sequence 891

Sequence 892

Sequence 893

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACACAGTTTGGAAGTTT
AGGCAAAAGTCATTTCTTCCCTATATTTTGTCATGCTTATCTCCTGTCTCTTTCTGTTTT
ACAGATTAGCAATAAACTCCTTAAAACCCAAAAGGTTTGGGCTTCTGTTCCTTTCACTTG
CAGTCAGACATGGAGTTAGTGGTAGAAGAAACAGAAGGGGTAACCTGCATGGTGACAGCT
ACTGAGGGGATAGGAAAGCAGGCTGAGTCCCTGGGGCCAGTGGTTACCAAAGCCAA
GGAGAGGGCAAGGGAGCCCAGTGGGCCTGG

Sequence 894

Sequence 895

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAAGGAGTAGTCTAAAACAA

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Sequence 896

Sequence 897

Sequence 899

Sequence 900

GCTNCACCGCGGTGGCGGCCCCCGGGCAGGTACCCTAAATGTTAAACTGAGGGATGAGT GAAACAATATCAGGATTAATAAATAAACACATTCTTGAATTCCATCACTTAATAGAAGTG GCCATTTGAATGCTGGCAGGTNGGAAGAAAAGAGGAGGACAAAGAACCCCAAAAGTTTGG CATCATAACTACTGCCACAAG

Sequence 901

GGCAGGTACCCACCTCCTCGGTCACCCACAGAGCCACCAAAGATTCCATGTCCCAGAGCT

TABLE 1 144/467

TCCCATAGCAGACCTGAAAAGTCCATGACCTGAGCTTTGGCCATGGTAGTGGAGTGGAAC AGGAAATAGTCCAGCAGAGGGGGGGGGAAGGGGGGAGAGGGAGAGAATAAGGGAGACCTGGACTCTTTTGGGAAAAGGAACCAAGCTCATAGCAATTTGGCTGATNAC ACAATCAGATTTTTCCAGGTTAAGCTTCCTTTCTG

Sequence 903

CCGCGGTGGCGGCCGAGGTACCATCTACTGAATGCCCAGTTTTGATCTATTTCTAAATGG
AGCAAACCAATTCCATCTCCTAGAGCTGGAGACTGTATCCAGGCAGTGTGTGGACAGAAC
GGACAATCTTTTCTGCCAAGGGCCTATTTGAGTGGAGCACCCCCACACGGGTTAGACGGG
TCGGCACGGGGCTGGTGGGTGAGGAACTCAGGGGTCAGTGCAAGCTGCAGACCCTCATTT
GGGGAACGCTCTCAGCACAATGCTCTTACAACTACAGGGTGCACTCCAAAATGGAGTTCA
AGGAAAAAAAGGCTAATGAGAAATAAAATCTGAAAAAAATAACTTAAAAAGTTTTGCT
Sequence 904

CCGGGCAGGTACGCGGGGGCCCTTTGGATACCTGCACTCCCCATCACCGCACTCCCCATC
GTGGCACTTCCCTTGTTGCAGTTTTATGGAGTGTGCGTCTGGCTCCCCAACTAGACTTGA
ACCGCTTGGGTGCATAACTCGGGACTTGACCATTTGCGTCTCCCTACGGCCAGCTCAGCC
TCCGCACACAGGGACCTGCAGAGAGTGGATGTAGCCACTGCCCCAGCGTCCCTGGGCTCT
GAAGAGAAGCCATTGCCCTTCAAGAGCCACCCTCATTTCCTGGGCACTGGTTTGGAAAAA
ACGAAGAAAAAGAGACACCCAGCTCACCTCCA

Sequence 905

CTCCACCGCGGTGGCGCCCCCGGGCAGGTACGCNGGGCAACTCATTCATGATATTGGG AGAAAAGCAAAACTGCAACAAAATCTCAAACCCTTTCTGCAGCAGCAGATGGCA AACAGTGATCAGAGGAGAAGGACCCTTCCAGCATTAGAAGATTTCCAAAAGGCTGTTCCAG TAGGGGCTGTGGGCTTCTGGGAGCCCAGATGCCCCCTGATGGTATATTTGAGTTTGTGAG GTGGAGGCCAGGTGGCAAGANACTGCNNGCCAATGTCAATGAAAAGCCTGGGAGGAAAAA GAGATTTCTGGGA

Sequence 906

Sequence 907

Sequence 908

AGGTACTTCCCTGAGCAGTCGAAGTGGATGCCCAGACCAATGGCCAGTGCTAATATCAAT GCAATGATCCCAATGACGATGATTGGAAAAACTTCAATGGCAGCAGTGACAGGATCTGT GCAGCAACAGCATCTGCATCTGGTGCAACAGGACTTATTTTCAAATCATCAAGGCCAAAA AGCGATCGGAATGAGAAGGGGGCTTCAACAGCAGGCGGATCATTTTCCCCCATGGTGACT ATTTCAGGACCTCTGACATCCGGCTCCGCCTCCACCTCTACCTCATAATTCCCGAGTCCC AAAAATGTAGATGGCACCACGGAAGAGATAGTAGGCCACAGTGTTACTGGCTTCCCATA Sequence 909

TABLE 1 145/467

GAAATTAAAAAGAGACTAAGAATATTACAAACAACTTTATTTCATTTAGATGAAATGGAC AAATTTATTTAAAACACAATTCGCCAAAATTGACAGAAGTGGAAGTAGAAAATCTATTT CTGTATTTATTAAAGATACTGAATCTATAATTAAAAAATATCTTCACACAGAAAATTACAG TTTCAAATG

Sequence 910

Sequence 911

AGGTACAGATCACTATGGCTTGTCTTTTCTCCTAACTAATGTAAAATTCCCAATAATTCA
TAACTTGTATGAGGACAACAGTTGTGTGAATCTACCCTGGTCCTTCTGATNATTTTTAAT
TTTTTNATTTTTTTTTTTTTTGGGGACAGAGTCGTGCTGTTATCGCCCGGGCTGGAGTGCA
GTGGCATGATCTCGGCTCACTGCAACCTCCACCTCCAGGTTCCAGCAACTCTCCTGCCT
CAGCTTCCCGAGTAGCTGGAATTACTGGTGCCCACTACCACACCCGGCTAATTTTTTGTA
TTTTTAGTAGAGATTGGGGGTTTCACCATGTTGGCCAGGCTGGTCTTGGACTC

AGGTACAAATTGTCGTTTTTATTCCTCTTATTGGGATATCATTTTAAAAACTTTATTGGG
TTTTTATTGTTGTTGTTGATCCCTAACCCTACAAAGAGCCTTCCTATTCCCCTCGCTGT
TGGAGCAAACCATTATACCTTACTTCCAGCAAGCAAAGTGCTTTGACTTCTTGCTTCAGT
CATCAGCCAGCAAGAGGGAACAAAACTGTTCTTTTGCATTTTGCCGCTGAGATATGGCAT
TGCACTGCTTATA

Sequence 913

Sequence 914

CGCCCGGGCAGGTACGCGGGGACTTGACTTAAACTCTGGGGCCCGGGAGGCCGCCGGTTT TCTCCCCGCTTGCCGGGGTGGTCCTCTTCCCTTTGTCGGACCAAAGAAGTAAACACTGTG TGGAGAGGGACTGCGTGTTTGGAGGGAAATGGGAATGTACCT

Sequence 916

CCCCGCGTCCGCTCTCTGTCGGGGTCCCCTCCATCTCGCTGCTGCTGAAGGCCGCGAGGG CGGCGCGATGGCGAGGCGCGCTGTTGCTGCTGCCTGAGGCGGCGGGGGGGACG CTAGGGAAAAGCTGGCTCTCTGGGATCGGAGACCGGACACGACGCGCCGCTGACCGACA GGCAGACGGACTCGGTATTGGAGCTGAAGGCGGCGGCAGAGAACTTGCCGGTGCCAGCTG AGCTTCCAATTGAAGACTTGTGCAGTTTAACATCCCAGTCACTGCCCATTGAACTGACTT CAGTAGTGCCTGAATCTACAGAAGACATTCTCTTGAAGGGCTTCACTTCCTTAGGAATGG AAGAAGAAAGAATTGAAACCGCACAGCAGTTTTTTCTCATGGTTTGCAAAGCTGCAAACT CAGATGGATCAAGATGAAGGAACTAAATATAGGAGCAGTGTGATGCTATATTGAATGATG TAAACAGTGCTCTTCAGCATCTGGAGTC

TABLE 1 146/467

Sequence 917

GGCTGTGGCCAAGAAACGCAGGGACCGCTCTCCCCCGGGCTTTCGAAATCTTCACAGA CAATAAAACCTATGTCTTTAAGGCCAAGGATGAGAAGAATGCAGAAGAATGGCTCCAGTG CATCAACGTGGCAGTTGCCCAAGCCAAAGAAAGGGAAAGTAGAGAAGTAACCACATATCT GTAGGGAATTTATAAGTCAGCCATGACAATTATACACCACAGGCATTGTATTATCATTGC CAATGTCAAGAAAAAGAGCTAAATTTACCAAGCCATGGTTGGNTTTTTACTAAATACCAT GGGAATTTGTTGGTCCTTTAAGAAGAAGGGCCTTAAAATGGCAGGGATTTCTTAGTNAAA TGNCAATACTCTAACAGCTTTAGTATTGACTTTAGAATATCTGATGCCCACAAAAATT AAATAAAAGGGNTTNGAGGAGGTTTGCCCNAAATAAGTGNGGGGCCCGGAGGGGAA Sequence 918

AGTCNCCACGCGTCCGCGGACGCGTGGGCGAGTGCCCAGTGACCCTTTACGGGGGTAGCT
TTTACTCCGCACTCTCAGCCCCTCACCCCTCCCTCAAGGCCCGGATTGACCATTTC
CTGCTCCAGCACTCCATCCCTGGCTGCCACCTGCTTGGGAGAGCACAGACGGCATTGGCA
GTGATCCCTTCTTCCATTGTTCTGCCCTCTCAGAAAAGGAAGATAGAGCAGGCTGAACAT
GTCCCAGACAGTAACTTTGGTGTAAATGCTTCCTGTTTTTCTGCCACAAGCCCTTTGGTC
TTACCCACTACCTCAGAGCACACTGCTAAGAAAATGAAAGCCACCAATGAGCCCAGCCTG
ACACATATGGGACTGCTCGACAGGTCCACTGTCCCACGAGCAGAAGCTGGTCACAAAGCT
TGGGAAAT

Sequence 919

GGGAGTCGACCACGCGTCCGCGACCGTGGCCAGTGACCCTTTCACGGGGG
TAGCTTTTACTCCGCACTCTCAGCCCCTGCCTCACCCCTCCAAGGCCCGGATTGACC
ATTTCCTGCTCCAGCACTCCATCCTGGCTGCCACCTGCTTGGGAGAGCACAGACGGCAT
TGGCAGTGATCCCTTCTTCCATTGTTCTGCCCTCTCAGAAAAGGAAGATAGAGCAGGCTG
AACATGTCCCAGACAGTAACTTTGGTGTAAATGCTTCCTGTTTTTCTGCCACAAGCCCTT
TGGTCTTACCCACTACCTCAGAGCACACTGCTAAGAAAATGAAAGCCACCAATGAGCCCA
GCCTGACACATATGGACTGCTCGACAGGTNCACTGTCCCACGAGCAGAAGCTTGTCACAA
AGCTTGGAA

Sequence 920

Sequence 922

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Sequence 923

Sequence 924

Sequence 926

Sequence 927

CGCGTCCGGTCATATACAATGTCATTGTTTGGGACCCGTTTCTAAATACATCTGCTGCCT ACATTCCTGCTCACACATACGCTTGCAGCTTTGAGGCAGGAGAGGGTAGTTGTGCTTCCC TAGGAAGAGTGTCTTCCAAAGTGTTCTTCACTCTTTTTTGCCCTGCTTGGTTTCTTCATTT GTTTCTTTGGACACAGATTCTGGAÁAACAGAATTATTCTTCATAGGCTTTATCATCATGG GATTCTTCTTTTATATACTGATTACAAGACTGACACCTATCAAAGTATGATGTGAATCTG ATTCTGACAGCTGTCACTGGAAGCGTCNGTGGAATGTTCTTGGTAGCTGTGTGGCCG ATTTGGAATCCTCTCGATCTGCATGCTCTGTGTTGGACTAGTGCTGGGGGTCCTCATCTC

TABLE 1 148/467

GGTCANGTGACTTTCTTTACTCCACTGGGAAACCTAAAGAATTTTTTCATGATGATTGGG TGTATTCTGGGTCACTTTCTCTTGCCATAAGCTATNCTCATTCCAGTAGTTT Sequence 928

Sequence 929

CGACGCCANGGCGCCTCCGAGTTCCCCGCCAGGACTCGGAGGGCCAGGAGGGCGCGACC
TGGGTGGATATTTTTGTTGGACGCGCAACTCTTGGGGTGGCCCGGGAGCGGCGAAACC
GAGCGAGAACCAGGAGGCGCTGCGCAGAAGGAGGCCCGGGGGCTCCGAGGCGTTGAGG
GGCTCGATCTGCGTTCTGGGGTTGGCAGCCGAGAGGCCCGCGGTCCCTGAGTGCCAGAGGT
GGTGGTGTTGCTTATCTTCTGGAACCCCATGCAGCCAGATCCCAGGCCTAGCGGGGCTGG
GGCCTGCTGCCGATTCCTGCCCCTGCAGTCACAGTGCCCTGAGGGGGCAGGGGACGCGGT
GATGTACGCCTCCACTGAGTGCAAGGCGAGGTGACGCCCTCCCAGCATGGCAACCGCAC
CTTCAGCTACACCCTGNAGGGATCATACCAAGCAGGCCTTTGG
Sequence 930

Sequence 931

CACGCGTCCGTGGAGTATGTGCCATCTGCCAAAGTGGAGGTGGTGGAGGAGCGCCAGGCC
ATCCCTCTAGACGAGAACGAGGGCATCTATGTGCAGGATGTCAAGACCGGAAAGGTGCGC
GCTGTGATTGGAAGCACCTACATGCTGACCCAGGACGAAGTCCTGTGGGAGAAAGAGCTG
CCTCCCGGGGTGGAGGAGCTGCTGAACAAGGGGCAGGACCCTCTGGCAGACAGGGGTGAG
AAGGACACAGCTAAGAGCCTCCAGCCCTTGGCGCCCCGGAACAAGACCCGTGTGGTCAAG
CTACCCGCGTGCCCCAC

Sequence 932

TABLE 1 149/467

CATCCCAGCTCAAGGTGGTCAGAGCTAGACCTTCTTATTCTGTTGGGGACGGCGGGCCAC GTCTTGAGCCTGGGCGCAGCAGCTTCGTGGAGGAGGAGCACCAGACCTGGTACTTCCTT GTGAACACCCTGTGTCTAGCTCTGAGCCAAGAAACCTACAGAAACTACTTT Sequence 934

CCGTCCGGTTTTTTGTCTCAGAGTTCTTCAGGCTGTACAGGAAATGTGGTGCCGGCATCT GCTTCTGACGGAGTCTCACTCTGTCGCTCAGGCTGGAGTGCAGTGGCATGATCTCGGCTC ACTGCAACGTCCGCCTCCTGGGTTCAAGCCATTCTTCTGCCTCAGCCTCCCGAGTAGGTG GGACTACAGTGGCCATGTGTCTGAGATCTAACCAAGGGAACATGGGTGGAACTGATGTAA GCCACTTTGACACCACAAAACCTCCCATGGGTTCTCTCTTCTTCTTCTTCTGGTGTACTTGT TGGATGGAGAAGATGCTGAGAAATAGTGGGAAGTCCTAGGGGATGGAAGAACCCAGGATT CTGAATACTCCATTGGACCTTACGTTTTGGAATCAGGNATGATGCTGGCCTTCATAAAAT GAGTTATGGAGAAAGTCCCTCTTTTTCTGGTGTTTTGGAACANGTTTTCAGAAANGAATTT GNTACCCAGCTTCCNTCTTTTGTACC

Sequence 936

Sequence 937

GTCCGCCGCATGAGCTGTCCATGAAGGATGAGCTGCTTCAGTTCTACACCAGCGCTGCG GAGGAGAGTGAGCCCGAGTCCGTTTGCTCAACCCCGTTGAAGAGGAATGAGTCGTCCTCC TCAGTCCAGAATTACTTTCATTTGGATTCTCTTCAAAAGAAGCTGAAAGACCTTGAAGAG GAGAATGTTGTACTTCGATCCGAGGCCAGCCAGCTGAAGACAGAGACCATCACCTATGAG GAGAAGGAGCAGCAGCTGGTCAATGACTGCGTGAAGGAGCTGAGGGATGCCAATGTCCAG ATTGCTAGTATCTCAGAGGAACTGGCCAAGAAGACGGAAGATGCTNTCCGCCAGCAATGA GGAGATCACACA

Sequence 938

Sequence 939

CGTCCGGCCGGCGCGGCAGTGGCGGCCCGGCCTGCAGGAGCCCGACGGGGTCTCTG

TABLE 1 150/467

Sequence 940

Sequence 942

GTCCGGTTTTGAAACAGAAATGTAGGCATTAGACTTCCTGGGCGGCAGACAAACCAAAGA GCGGAAATTCATGCAGCCTGCAAAGCCATTGAACAAGCAAAGACTCAAAAACATCAATAAA CTGGTTCTGTATACAGACAGTATGTTTACGATAAATGGTAAGCTTTCACATTTGATTTCT TCTGTTTTCCAGTAACTGTGAAGGGAAATTGGTAGGAGGTGTTGTAACAGGGCAGGACC CAAATGGGAACGGGGGATGACATTGGTTTGTCAGGTACCGAGCAAAGAGTGAGGATTTT GGAGTCTCCCTTCTGCTGCTCTGATGTTTTCCACATGCTTATTTCTTTGCCAGGCACTGG AGATGCAGTCAAGAAGTGGGAAGTGGCTCTTACTTCTAGTCTGTGTGTATAAGTCACT TAAGATGGCCGTGTTGACTGCTTCTTTGGGAAATGCCCTGAATAGGAGCATGTAGGGGAT GCTTACCGAGGCTGGGGAAGG

Sequence 944

TABLE 1 151/467

CCTCGTTCTCCAACGGCTGCTACGAGGGCAAGCCTTCTCAGAGGAAGCCCAAGCATTAGG AAGCCCGCAGGC

Sequence 945

CGCGTCCGGCACGGGGGAGTCTGTGGTGGCCNGTTTACCTGGGCATCTGGCTGAGAGGAA
GAAAGGCCAACCTGATCCTGAGGGGACCCAGACATATCCTTTGCACTGTCCCTAGAGGGG
CGATGAGCTTTGCAGCATTAAAAAATGGTGAAGGGGGGAAATATTTTGAACCAAAGACCA
AATGTTAGGCCGCCGTTATATTTGCAGAAGCTTTGAGAACCATGCGTATAGCCTCCTGCA
TTCTCCCCTCTCCTAGGAGCTCTTTTGTCTCTGTCCTTACGAGGCGTCATACAGAGGCAG
TGGGGTGGGCACAGATGAGCAGAGTGGATGGTTCGGTGGGTCCCCACGAGGGCGAGTGGT
GGTCATATGTGATGGCACCGTGTTCACACCCCTCCTGTGTACCCCCCCAGGGTCACCCG
AAGTCCCCACACGCTGGCTCTCCACACCCCTCCTGTTCCAGAAAGCATGTCCCG
Sequence 946

TCGACCNCGCGTCCGGCACTCCCTCTGGCCGGCCCAGGGCGCCTTCAGCCCAACCTCCCC
AGCCCCACGGGCCCACGGAACCCGCTCGATCTCGCCGCCAACTGGTAGACATGGAGACC
CCTGCCTGGCCCCGGGTCCCCGGGCCCCGAGACCGCCGTCGCTCGGACGCTCCTGCTCGGC
TGGGTCTTCGCCCAGGTGGCCGCGCTTCAGGCACTACAATACTGTGGCAGCATATAAT
TTAACTTGGAAATCAACTAATTTCAAGACAATTTTGGAGTGGGAACCCAAACCCGTCAAT
CAAGTCTACACTGTTCAAATAAGCACTAAGTCAGGGAGATTGGAAAAGCAAATGCTTTTA
CAC

Sequence 947

Sequence 948

Sequence 949

TTNGGGAGTCGCCACGCGTCCGGCCGGCGACGGCGAAGTGGCGGCCCGGCCTGCAGGA

TABLE 1 152/467

GCCCGACGGGGTCTCTGCCATGGGGGAGTGACGCGCCTGCACCCGCTGTTCCGCGGCAGC GGCGAGACATGAGGAGACCCCGCGACAGGGGCAGCGGCGGCGGCTCGTGAGCCCCGGGAT GGAGGAGAAATACGGCGGGGACGTGCTGGCCGGCCCCGGCGGCGGCGGCGGCCTTGGGCC GGTGGACGTACCCAGCGCTCGATTAACAAAATATATTGTGTTACTATGTTTCACTAAATT TTTGAAGGCTGTGGGACTTTTCGAATCATATGATCTCCTAAAAGCTGTTCACATTGTTCA GTTCATTTTTATATTAAAACTTGGGACTGCATTTTTTATGGTTTTTCAAAAGCCAT TTTCTTCTGGGAAAAC

Sequence 951

Sequence 952

Sequence 954

CGTCCGGACCCTTATTAAGAATATCCCAGGAAGATGGTGATGAACAGCCTCAGTTTACTT
TTCCACCAGATGAATTCACTAGCAAAAAAATTACAACAAAAAATATTACAGCAGATTGAGG
AACCATTGGCACTGGTGTGAACAATTAACCAGCAAATGTCCTTTTCTAATACCATTTGAA
ACTAGACAGCTTTATTTCACATGTACAGCATTTGGCGCCTCAAGAGCAATAGTATGGTTA
CAGAACCGACGTGAAGCCACTGTGGAGCGAACGAGAACCACAAGCAGTGTTAGGCGAGAT
GACCCTGGAGAGTTTCGAGTTGGTCGTCTCAAGCATGAAAGAGTAAAAGTTCCACGTGGC
GAGTCACTGATGGAATGGGCTGAGAATGTCATGCAAATACATGCAGATCGGAAATCAGTT
CTTGAGGTTGAATTTTTAGGAGAAAGAAGAACTGGCTTGGGACCCACATTAGAGTTTTAT
GCTCTGGTG

Sequence 955

TABLE 1 153/467

GGGGTAGAGATCCGGAGCGCCACCGGCAAAGAGGTGTTGCAGAACCTCGGCCCCAAGGAC AAGAGTGACCGTCTNCTTATCAAGGGAGGCAGAATCGTCAATGATGATCAGTCCTTTTAT GCTGATATTTACATGGAAGATGGCTTAATAAAACAAATTGGAGACAATCTGATTGTTCCT GGAGGAGTGAAGACCATTGAAGCC

Sequence 956

Sequence 957

Sequence 959

Sequence 960

CCACGCGTCCGCGGACGCGTGGGGCCGGGACAACTGGTCTTATCACGGAGGCTGGGGCCA
NGGCAGCCCTTCGGTTCGGGTGGGCCCATGGACCCCAGTCCAACGCCGAGGGAATAGGAC
CATCCAAAAGCGGAACCTTCGCCTCAGAAAAAGGGTGCGGGACCCCTCCTCACCGTGCGG
TCACGCGTGGACCCTGCCAGCAGCCAGGCCATGGAGCTCTCTGATGTCACCCTCATTGAG
GGTGTGGGTAATGAGGTGATGGTGGCAGGTGTNGGTTGGTNGCTGATTCTAGCCTTG
GTCCTAGCTTGGCTCTCTACCTACTTAGCAGACAGCGGTAGCAACCAGCTCCTGGGCGCT
NTTGTGTCAAGCAGGCGACACACCGTCCTNCACCTGGGGCATGTGGACCACCTGNTGGG
CAGGCCAAGGCNNCCCCGAAGCCAACTGA

Sequence 961

NCCCGCGTCCGGGAGGCTCCATGTTGTCCCCTCAGCGAGTGGCAGCAGCTGCCTCAAGA

TABLE 1 . 154/467

GGAGCAGATGATGCCATGGAGAGCAGCAAGCCTGGTCCAGTGCAGGTTGTTTTGGTTCAG
AAAGATCAACATTCCTTTGAGCTAGATGAGAAAGCCTTGGCCAGCATCCTCTTGCAGGAC
CACATCCGAGATCTTGATGTGGTGGTGGTTTCAGTGGCTGGTGCCTTCCGAAAGGGCAAG
TCCTTCATTCTGGATTTTATGCTACGATACTTATATTCTCAGAAGGAAAGTGGCCATTCA
AATTGGTTGGGTGACCCAGAAGAACCGTTAACAGGATTTTCCTGGAGAGGGGGATCTGAT
CCAGAAACCACTGGGATTCAAATCTGGAGTGAAGTTTTCACTGTGGAGAAGCCAGGTGGG
AAGAAGGTTTGCAGTTGTTTCTGATGGATACCCAGGGGGGCAT

Sequence 962

Sequence 963

Sequence 964

Sequence 965

TGCGCATGCGCGGAGCGCGCGCGCGCGCGGTTGGCCGTTTGCTTCCGCCCTGGA TCCGCCGCACTCCGCGATCAGACCGCTCTGTGCCGCGAGCCGCCGTGAGCACTCGGATT CAAGCCGGCGCCAACGAGTCCGGGGGCATCGCCCGCAGCGGCCAAGCTCATGGCCGGCTG AGCGGGACGCCGCTNCGCCTCAGCCACCGCCGCCGCCGCCGCCGCTTCTTCTCCTCAGCCG GCGGCGCCCGGGCCCAGCAACCATGGCTGAAGACTACTGGGACGGCGCCTGCGGCGAA CAGGAGGAGAAAGGGAGGTCGCGCGGCCTCATTCCGGGCCGCCCCCAGGCGCCCCCC GCCGCCCCGCGGCTCTGAGGTTGCTCGCGCGCCCCC

Sequence 966

TGGAAAATNTTTTGGAAAAAATTACCCTTGGGACCTTGNTTTTNAANCCCNAGGTTCCN GTTNNGGCAAATAAAANAATGNNNGACCCGGGATTTNGGGNTTNNAAACCGGGGGTTTTT AATTTCCCCNNNNCNNGGGNCCTTTTTTTTTTNCCNCCCCCNCAAGGGGGNTTTGGGAAAN NAAANCCCCCCCTTTTTTTTTTNGGGGGNGAAANTTCCCCGGGTNNNNGCCNTTTTTTT TTTTTAAA

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Sequence 967

GTCCGCGAGGCTCCGCACCAGCCGCGCTTCTGTCCGCCTGCAGGGCATTCCAGAAAGATG
AGGATATTTGCTGTCTTTATATTCATGACCTACTGGCATTTGCTGAACGCATTTACTGTC
ACGGTTCCCAAGGACCTATATGTGGTAGAGTATGGTAGCAATATGACAATTGAATGCAAA
TTCCCAGTAGAAAAACAATTAGACCTGGCTGCACTAATTGTCTATTGGGAAATGGAGGAT
AAGAACATTATTCAATTTGTGCATGGAGAGGAAGACCTGAAGGTTCAGCATAGTAGCTAC
AGACAGAGGGCCCGGCTGTTGAAGGACCAGCTCTCCCTGGGAAATGCTGCACTTCAGATC
ACAGATGTGAAATTGCAGGATGCAGGGGGTGTACCGCTGCATGATCAGCTATGGGTGGTG
CCGACTACAAGCGAATTACTGTGAAAGTCAATGCCCCATACAACAAAATCAACCAAAGA
Sequence 968

Sequence 970

Sequence 971

CCTGCCAGTGGTGAGCACCTTCGGCCTCCAGGTGCCTTTCTTCTTCTTCGCGGCCATNTG CTTGGTGAGCCTGGTGTTCACAGGCTGCTGTGTGCCCGAAACCAAAGGGACGTCCNTGGA GCAAATCCGAGTCCTTTTTCCGCACGGGGAGAAGGTCCTTCTTGCGCTAGGTCAAGGTCC CCGCCTGGAGGGGGCCAAACCCCCA

Sequence 972

GCGTCCGCGGACGCGTGGGCGGACGCGTGGGTCAGCCTCCACCTGGAAGAGAGACTANGGG CCGGGCAGGCCGGCCACCCCGCCCGGCCCGACGCCCCGCATGCCCCGAAGTCC CTGGCGCCCACCCGGCCCTGCGTGTGACCCGCGGGTCGATACCTGGCAGCCCCA GTGCTGGGGCGCCCGGGCCTGCTCGCCCAGGAGGAGAGCGAGGGCCCCACACTGAGTCT CTTGAAGCCTCACGTTTCCCTGGGGGGGTGCTGCATCGTCGGGTGTCCCTCACCCCACCT WO 01/070979

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GGGGAACCTCTGTCTTCAGGTCACCCCTTTTCAGGGGCCTGG

Sequence 973

Sequence 974

Sequence 976

Sequence 977

NCTCCAACAATTATGGCTCATCCTTCCTTTTACTCTGTCTCACCTCCTTTAGGTGAGTAC
TTCCTTAAATAAGTGCTAAACATACATANACGGAACTNGAAAGCTTTGGTTAGCCTTGCC
TTAGGTAATCAGCCTAGTTTACACTGTTTCCAGGGAGTAGTTGAATTACTATAAACCATT
AGCCACTTGTCTCTGCACCATTTATCACACCAGGACAGGGTCTCTCAACCTGGGCGCTAC
TGTCATTTGGGGCCAGGTGATTCTTCCTTGCAGGGGCTGTCCTGTACCTTGTAGGACAGC
AGCCCTGTCCTAGAAGGTATGTTTAGCAGCATTCCTGGCCTCTAGCTACCCGATGCCAGA
GCATGCTCCCCCCGCAGTCATGACAATCAAAAAATGTCTCCAGACATTGTCAAATGCCTC
CTGGGGGGCAGTATTTCTCAAGCACTTTTAAGCAAAGGTAAGTATTCATACAAGAAATTT
AGGGGGAAAAAACATTGGTTAAATAAAAGCTATGTGTCCTATTCAACAATATTTTT
Sequence 978

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Sequence 979

AGGCTGNTACGAAGCGAGCTTGGGAGGAGCAGCTGGCCTGCGGGGCAGAGGAGCATCCCG
TCTACCANGTCCCAAGCGTGTGGCCCGCGGGTCATGGNCAAAGGAGAAGGCNCCGANAG
CGGCTCCNCGGCGGGGCTGNTACCCACCAGCATCCTCCAAAGCACTGAACGCCCGGCCCA
GGTGAAGAAAGAACCGAAAAAGAAGAAACAACAGTTGTCTGTTTGCAACAAGCTTTGCTA
TGCACTTGGGGGAGCCCCCTACCAGGTGACGGCCTTTCCTCATCATCCTGCTTCANAT
CTACCTATTGGATGTGGCTCAGGTGGGCCCTTTCTCTCCTTCATCATCCTGNTTGTGGG
CCGANCCTGGGATGCCATCACAGACCCCCTGGTGGGCCTCTGCATCAGCAAATNCCC
Sequence 980

Sequence 981

TNGGGAGTCGACCCGCGTCCGGTTTTTGTGAGGCAGTGAGACCTAAGGTAACCTTTATC
AAAAGGATGGAGTTGGGAAAAGGAAAACTACTCAGGACTGGACTGAATGCGTTGCATCAA
GCAGTGCATCCGATCCATGGCCTTGCCTGGACCGATGGGAATCAAGTTGTCCTAACTGAT
TTGCGGCTTCACAGTGGAGAGGTCAAGTTTGGGGACTCCAAAGTCATTGGACAGTTTGAA
TGTGTCTGTGGGTTGTCCTGGGCCCCACCTGTTGCAGATGATACACCTGTTCTACTCGCT
GTCCAGCATGAGAAGCATGTCACTGTGTGGCAGCTGTGTCCCAGCCCTATGGAGTCAAGC
AAATGGCTTGACGTCTCAGACTTGTGAGATTAGGAGGGATCACTACCTATCCTTCCCCAG
GGCTGTGTGTGGCACCCAAA

Sequence 983

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CTGCAGTGGGGATTTATTTTT

Sequence 984

Sequence 985

Sequence 986

CGCCACGCGTCCGCGTACGCGTGGGCGCGACCGAGCGTGCGGACTGGCCTCCCAAGCGTG GGGCGACAAGCTGCCGGAGCTGCAATGGGCCGCGGCTGGGGATTCTTGTTTGGCCTCCTG GGCGCCGTGTGGCTCAGCTCGGGCCACGGAGAGGAGCAGCCCCCGGAGACAGCGGCA CAGAGGTGCTTCTGCCAGGTTAGTGGTTACTTGGATGATTGTACCTGTGATGTTGAAACC ATTGATAGATTTAATAACTACAGGCTTTTCCCAAGACTACAAAAACTTCTTGAAAGTGAC TACTTTAGGTATTACAAGGTAAACCTGAAGAGGCCCGTGTCCTTTCTGGAATGACATCAG CCAGTGTGGAAGAAGGGACT

Sequence 987

GGTCGCCCGCGTCCGTAGCAGTTACATCTACGAGGCTATTATGGATTGGAGGATGAGAA GGGAACTGCATGTACCTCAACAAGGCGTCGGTCAACACCCGCGAAGTTTGGCAGGCTTGAC AAGTGGAGTTTTTGAATCTATAATGGTTCAAGTTTTGAGACAGGAAGAACAGCTGAGAGC AAAAGAAGAAAAAAGGCTTCGGGAGCAGGAAAGAAAGAAGCAGAAGAAGCTAGTCAAAA GGAAATAGAAGAATGGGAAAGAAAACTTCTAGCTCAAGCAGCTCCAACTTGTATGGAGAC CATGTGGGAAATTCCAGCTATTGGGCATTTCCTTTGTTTAGCTCAGCAAATTCTAAATTT GCCAGAAATAGTCTTTTACCGAACTGGAACCGTTGTCTTCTGATGCCTCAGTGTAATGCT

Sequence 988

Sequence 989

GTCGCCCACGCGTCCGTTGTCGATGGACCTGCTTGCAAAAGGCCAGCTCTGTTGCATTCCCAATTTTTGACACCACCTCAAACACCAACGCCCGGGGAGAGCATGGAAGATGTTC

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GTCCGCTGGGACCTCCTCTTTGGGGTCCCCATGAACCCTTCCAGTTCAACCTTTCA
GGACGGAACCCCCAGAAACAGGCCCGGACCTCCTNCTCTACCACCCCCAATCGAAAGACA
ATGCCTGTGGAAGACAAGTCAGACCCCCCAGAGGGGTCTGAGGAAGCCGCAGAGCCCCGG
ATGGACACACCAGAAGACCAAGATTTACCGCCCTGCCCAGAGGACATCGCCAAGGAAAAA
CGCACTCCAGCACCTGAGCCTGAGCCTTGTGAGGCGTCCGAGCTGCCAGCAAAGAGATTG
AGGAGCTCAGAAGAGCCCACAGAGAAGGAACCTCCAGGGCAGTTACAGGTGAAGGCCCAG
CCGCAGGCC

Sequence 991

Sequence 992

Sequence 993

CGCGTCCGGGCAGGAGCACCACTCAAGGAGCTACACCCCTTGCATCGGCTTGACCGCCTT ACCTCAGGGGTGCTTATGTTTGCCAAGACAGCTGCAGTCTNTGAGAGAATTCACGAGCAG GTTCGGGACCGGCAGCTGGAGAAGGAGTACGTGTGCCGGGTGGAAGGGGAGTTCCCCACT GAGGAAGTGACCTGTAAAGAACCCATCTTAGTGGTGTCTTACAAAGTAGGGGTGTGCCGT GTAGATCCCCGGGCAAGCCCTGTGAGACAGTGTTCCAGAGGCTAAGCTACAATGGCCAG TCCAGTGTGGTACGGTGCCGGCCACTCACAGGCCGCACACACCAGATTCGAGTCCACCTT CAGTTCTTGGGCCATCCCATTCTCAACGACCCCATCTACAACTCAGTTGCCTTGGGGTCC TTCTCGAGGCCGGGCGGCTACATTCCCAAGACAAACGAGGAGTTGCTACGGGACCTGG Sequence 994

ACGCGTCCGCGACCGCTGGGCATGCGGGTGTTGGCGCGGTATCCCCGCCCTGCCCAGCAT CTGCCCCACGTTTCTTCAGGCTAAACTACCGGGATCCCGGGCTTCTTCCTAAAGTAAAAC TCGCTCCGGAAAGGCCAACAGTCCAGCGGCCAGACGGGCACCTGGGAACGCGGGCCTAAC GCGTACTGGAGACGGAGCCCGGCACTGCGCCCCTCCTCCCCGCCGGAGACTGCG TGCTAAGCTCAGCAAAGCCCCGCTGTGGAGACGGAGCCATGTCGCCCATTACCTAATGAA ACTGAGAAGGGAGACTCAGTCTCTTCTAGCCCCGAGCGCAAGCTCTGCTGGACTTGGC ATCGTCCGCCCTCCACGATCCCACACTCCGGGTTTTCCCCATTCCCAGCTCGGCTGCAAC CGAGAGACAGACGGAAGAAAC

Sequence 995

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Sequence 996

Sequence 997

Sequence 998

Sequence 999

Sequence 1000

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Sequence 1001

Sequence 1002

Sequence 1004

Sequence 1006

ACCACGCGTCCGGAAAAGCCCGGAAGTGCCACGGGACTTCCTGTCTAAGGAAGAGCCTC
GTGAAGCTCCTCCACTGGGGAGTCAGTGGCCTTCGTTGTATCTGCCCCGCTTGTCCACCT
CCTAGAGTGAATCCCCGCCTGGAGGCTGGGACACTAACCAAGAAGTGGCACATGCATAT
CACGGGAGCAATGTTGCCGCTGTACGGAGAGTGCTGGACCGAGGGGAGCTGGGAGCAGGT
ACTGCCTCCATCTGANGCCGTCCTTTGAAGGGAGAACCTGGGGTAGGGTTCGAGGAGCCN
GCGAGAACTGTGCACCTCCTCGGGAGGAGCCCCCCTCCTGTGCTTCCCCCTCCC
TTCAATATGCTGGGGGCGGAGACCCTGGCCTCCAAAGTGCAATTCCGGGACCCCAAATCC
CAGCGGACGCACCAGGCTTTAGGTGGGCCGTCAAGTTGNTGTGTGCCCCCTGGCTTCTACA

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CCCCGGGACCCCCTTCCG

Sequence 1007

GCGTCCGGGCNGCGAGTTTTGTCCATAACGTGGGCAACCGCGCAGCTGGAGGATGGCCT CACTCGGGCCTGCCGCAGCTGGGGAGCCAGGCGTCGGGGGCCCCG CGGGGCCGCCGCCGCCCTCACCGTCCTCTCTGGGGCCCCTGCTCCCCCTGCAGCGGG AACCTCTCTACAACTGGCAGGCGACCAAGGCGTCGCTGAAGGAGCGCTTCGCCTTCCTCT TCAACTCGGACTGCTGCGATGTGCGCTTCGTACTGGGCAAGTTGGCGGNGCCGCCCCG CTGGGGGCCCGCAGCGCATCCCCGCCCACCGCTTCGTGCTGCGGCCGCCGCCGCCTC TTTG

Sequence 1009

Sequence 1012

TABLE 1 163/467

Sequence 1013

Sequence 1014

GTCGCCCGCGTCCGCGGNCGCGTGGGGTGCTNGTCACCAGACTGCACCCTTGCCAGCAG CTTCGCAGCTCTCGAAGTAANTTATCGCANGATGGCCGGCGCCTCACCTAGGAGAACCAG GAAGGCAGGCCNCGCTAGAACGACGGNATTGAATTTTACTATTGNCAAAACAATCACATT CAAATTCATTCCACTTAAAACCTGAAAACATTGGACCACACAA Sequence 1015

CGCGTCCGCTTTCAGTGAAGAAAAGGGAATTACACATNGAATCGACACATCAGTAATACC
GATACAGTGAAATGGGCCTCTAATAAGAATTTNAGCGNGTTTTCTGATGTGCCATTTTT
TTGTCTTTTTAAAAATATACCATANTTATAAAANTGGNAAATANNTTTTTGNACACCAT
TTAAATTGACCCCCTTANAGNACNCTTGCCGTNATGNTGAAANGCTAGACCTATNGAAGC
TGNCTTGANGATATNTGTTTTTTTAAAAAAAATTTTTTACAACTNTACTTGTTGGAAAATA
TAATATGCACTATAAAAATATGATCNTATATCCTATTATCTATNATCTAAAAAACACTTCCT
TGGACNCATTTANACGTAAAATTAAAAATGGGTCTTTAANGAAGANTAATGGGGAGGCCC
CTTTTTTAAAACCTATGGNNCAATCTTTTTTATGNCAAAGGGGNGGACCATTTTATTAAAA

Sequence 1017

GCGTNCGCTGCGCCCGTGGGACCGGTGAAGTTCTGGCGACCCGGTACAGAGGGGCCAGGT GTAAGCATCTCTGAAGAGAGACAAAGTCTGGCTGAAAACTCTGGGACAACGGTTGTTTAC AACCCTTATGCTGCCCTTTCCATAGAGCAGCAGAGGCAGAAGCTGCCGGTATTCAAGCTT AGGAATCATATTTTATACTTGATAGAAAATTATCAGACAGTGGTGATTGTTGGTGAAACA GGATGTGGGAAGAGCACACAGATTCCTCAGTACCTTGCAGAAGCCGGCTGGACAGCTGAA GGAAGAGTGGTAGGAGTGACCCAGCCTCGAAGAGTGGCTGCTGTTACACATGATCTTTCT TNCCAAAGGTTGCAGGGAGAGAGAGCTGAAGAAAGGGGTGCAGTGCTGGGCCACCAGGTGG

Sequence 1018

AGTCGCCCGCGTCCGGTGGGAATCTTTCNACTTCTTGATCCATCTGGGAGAGAGACGT ACCATTATGTGCCCGAAATTCCGAAAAGTGTCCATAGCAGCTACCATCATCTATGCCTATG CCTGGCTGGTTCCTCTTGCACTCTGGGGTTTCCTCATGTGGAGAAACAGCAAAGTTATGA

TABLE 1 164/467

ACATCGTCTCCTATTCTGGAGATTGTGTGTGTCTATGGATATTCCCTCTTCATTT ATATCCCACCGCAATACTGTGGATTATCCCCCAGAAAGCTGTTCGTTGGATTCTAGT Sequence 1019

GGAGTCGCCACGCGTCCGGTGGCACGATCTTGGCCCACTGCAAGCTCCGCCTCCCAGGTT
CACGCTATTCTCCCGCCTCGGGAGCTGGGACAACAGGTGCCCGCCACCACGCTCGGCTAA
TTTTTTGTATTTTTAGTACAGACGGAGTTTCACCGTGTTGGCCAGGATGGTCTCGATCTC
CTGACCTCGTGATGCACCTGCCTTGACCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCA
CTGCGCCCGGCCAATAATTTTTTTTAGTTTAAGTTCATTTTTTGTCCCCGCTGATGAAAGTT
ACAGCAGCTGCCCAGTGCCTCTGTCCACACCCACCTCCCTGGTGTACTTGCCCCCTACAG
CAGCAGCCCAGATCCTCCCCTGGATTAAAATTGCAACTGGTGCCCTAACCCAAAACTTGA
GAAAAAATTCTCTATCACATCCACTCTTCTGGCATTTGTAGAATCTC

Sequence 1020

GTCCGGTNGATATATATTTTACCTCCTTAGTAATGCAAGAAGTGTTTGTGGGAAGCAGA
GAAGCAAGCAACTGTATTTCTTGTTCTCACCTAAGCATTACTGGAGGATAAGCCACATCA
GTCTACAAAGAGGTTTTCATACAAACATAATAAGATGTAAAATGGACCAAAAGTTGAAAG
CACATTCTTGCAAGTAAGCACCTGTTACTCTCCAAGCAACCATGGGTTTACCATATTTGG
GGATTTTTTGAACACTTAGNCACTTTCTTGCTCCCNAAGGGGACNTTTACAAAAAGTGNA
NACATTTTTGTANTGTNNCCCGTTATTAAAAAAGCTAACNTTTTGTAACCTNCTTGTTTT
CAAAAGGGCTTGGTNTTTTTGGACAAATTCAAAAATGGAAAAATGGATTTTCACCGTTT
TAAGCCTCAATTTTAAGCCCCAAGGTTCCCAAAAATTTTTTAANGAAAAAAGTTATTCGG
GTATTAGGTNGGNCCTGGGTTAAAAAAACCAAGAANAAAACCATTNAAAAACAAAGCCCATT
CAAAAATTCTTNTGGAAAAAAAA

Sequence 1021

Sequence 1022

CAGGGAGTCGACCCGCGTCCGAGCATCTTGGGGAATTTATATTCCTTTGTGAGAAATGT
TTTGATCATAAGCCTAGAATGATAAAGTAAAAGAAATAAAGATAATTCTACTGCTTGTTCT
CACCCGGTTACAAAGCATGAGTTTGAAGACAATAAGTGCCTTGTCCACATTTTGCGAGAG
ACAACAGTAAAATACTCCAAAATACGTTCTTTTCATGGTCAGTGTCAGCTTGATTTATGT
CGACATGAAGTTCGGTATGGCTGTTTAAGGGAAGATGAGTGCTTTTATGCCCATAGTCTT
GTGGAACTGAAAGTCTGGATAATGCAAAATGAAACAGGTATCTCACATGATGCTATTGCT
CAAGAGTCTAAACGATATTGGCAGAATTTGGAAGCAAATGTACCTGGAGCGCAGGTCTTG
GTAATCAAATAATGC

CNCGCGTCCGGCCAACCGCCGAGGAGCAGTGCCCTATTCAGCACAGTGCGCCAGGGCCAC TGGCAGATTGTTGATCTTTTACTCACCCATGGAGCTGATGTCAACATGGCAGACAAGCAG GGCCGCACTCCCCTGATGATGGCTGCTTCCGAAGGCCATCTAGGAACCGTGGACTTTCTG CTTGCACAAGGTGCCTCCATTGCTCTTATGGACAAAGAAGGATTGACAGCCCTCAGCTGG GCTTGTTTGAAGGGCCATCTCTCAGTAGTACGTTCTCTGGTGGATAACGGAGCTGCCACA GACCATGCTGACAAGAATGGCCGTACCCCACTGGATCTGGCAGCTTTCTATGGCGATGCT GAGGTGGTCCAGTTCCTGGTAGATCATGGGGCCATGATCGAGCACGTTGACTACAGTGGA ATGCGCCCTTTGGATAGGGCAGTGGGGTG

Sequence 1024

GTCGCCCCGCGTCCGAGAAGTCAGGGAGTGGAGGTTCTATAAGGAATTAACAGCTGAGGA

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Sequence 1025

GGAGTCGACCCACGCGTCCGCTCGACAGCCTCCGCCACATCCTCCACCTCTCTTGGTCCA
GCGAGCGTTGCCGGGCCAGGGTCAAGCGGAGGGCTCCGACGCGCGGACGAGCGAAGCG
CCGAGCCATGGCGCACCAAACGGGCATNCACGCCACGGGAAGAAGCTGAAGGAATTCTTT
GCCAAGGCACGGGCTGGCTCTGTGCGGCTCATCAAGGTTGTGATTNGAGGACCGAGCAGT
NTCGTGCCTGGGTGCNCTTCGCAAGGGAGCCAGNTAAGGCNCGCTNGGGGATCAGGGACT
ATTGAACAGGNGGCCCGTGGCTTGCNCACCTGCNTGGGACCGCCCCAGGCAGGCCCTGCN
TACCTGGCTCTACCGCGCTTCGACTNACAAGAAATGGCTCAGGGGNCTTTCGAAATGGGG
CTTCTTTCCTTCGCCCTTGGTTCCGCNCTNGAATAAACCTCCCCCCGTGGCGGCTTGAA
AGANTGCCTGTACCGCCGGGNCAATGCNGGGCCCCACAAGTGGAAAAAAGGGAAG
Sequence 1026

Sequence 1027

CGTCCGTAGTCTCTCGTGGCCCGGAAAAAAAAAAAGAAGAAGGTTGGGGCCAGTCACC CCCACATCCCTTTATGGAGGCTTCCAGATCATGGATCCTGTCACGCGCATCCCGGTGAAG AGAGTCCACCAACAGGCTTTGTATGGGGTCTCGCTCTGTTGCCCAGGCTGGAGTGCAGTG GTTCGATATGGCTCACTGCAGCCTCAGCCTCCCTGGGATCAAGTGATCCTNTCACCTCAG CCTCCCAAGTGGCAGGGACCGCAGGAAGGCCTGGACGACGGCCCGGACTTCCTCTCAGAA GAGGACCGCGGACTTAAAGCAATAAA

Sequence 1028

Sequence 1029

CGTCCGGAGAAGATGGGCCTCCCGGGCTCAGACTCACAGAAAGAGCTGGCCTGACCACCA GGCACCTCACTGGCACTGCTGACCCATCCCAGAAACACAATCTCAGGGACCCGAGCAGCT CCAAGGACGAGAGGATACAGCAGACACAACCTAATAGAGAGGGCGCCTGCAGCCTTAACC TCCACGGCCTTCGATACTTATGCAAGCCTGGTGTTGCTCCTGTCCTCAGAGTCATCCTGC

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Sequence 1031

Sequence 1032

TCGCCCGCGTCCGCAATTTCTTTTGAATTTCGATCACTTCTACATTCCCAGCTTGCCAC
ACTCTTTTTTGATGAAGTTGTGAAGCAGATGGTAGCTGCCTTTGAAAGAAGAGAGCATGTAA
GCTGTATGGTCCAGAAACAAATATACCTCGGGAGTTAATGCTTCATGAAGTCCATCACAC
ATAAAGGCAAAAAAGAACTGGTGCCACCTGCTTCTGACTTTAGTTTCACTTTTAGGA
AGTATTTTCATGACATGTTTTCAGAAGCCAGAAAGCATTTGTTAAACCGCAGCTTTGGTTA
TAAACCTGCACCATTGAAAATTTGCACATAGAATATAGACTCACTTGTACAATAATGGG
ATGTCATCACCATTGCTAGAAATACTGGCATGATTCTTCTGAGCAGAAGTTGAAACTGTAA
ATTTAAACCTTTTAATTATCACCTTACCT

Sequence 1033

Sequence 1034

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Sequence 1035

Sequence 1037

Sequence 1039

TGANATTAGCATCACTTCGTCTACTAAGAATCTTAATAGATGTAAAAATATCTTTTAAAA CATATGGTAGGATGGGTAAAATTTGGCAATACTATCCAGGAAGTCACTAAGTACAGATGA ACTGATTTAGTCCTAATTCCAAGAAGTGTGATTCCACCTACTTGACTAGAAATTTATACC

TABLE 1 168/467

TGGTAATAACTCCTTGTCCTTGAAGATTTTCAACTAAGGAAAACTGTTTTTCAGCAGGAC CTGATTATGCACTGCTATCTAGGTAGGGTCACTTATGGTTTTATAATATTTAATTGGA TTATAATATTCCTTTTTTCTTGTCTCTTTGGACAAAATCCTAGCTTTACTGTAATTTAAAA AGATGAGTTTAAAATTTCAGGCTTTAAAAACATACCAAACATTGATAAAAATGAAATCTA GATAAAAGTATTTTATCAATGTTCAGTTGCCTGGATTCAATAACTGTATTATGGTTATGT AAGGATAATATCTTAGGAAATCACATTATGGTATTAA

GTCGACCCGCGTCCGGTAGCTTAGTTGAGTAGATAATCTTTTGTTGTTTCCTCCTTGTA
ATATACAAGCCTTGGCTTCTGTGACATCCTCCTAGATTTCCCCCTGTCACTGTGG
CTTCTTCTCAGTCTCTGTCCATCCCTGGTGCTCCTGAAGGTTCTGTTCTCAGCCTTACAC
ACATTACCTGGGTGATCTCATTCTCTGCCATGACTTCACTTGCCATATATGTGCTGATTT
TCCCCAAATTCCTATTTCTCCCGACCTTTACATCTATTTTATTTGCAGGTCATATATCTA
ATAAGGAATTGATATCCAGTGTACATGTAGAACTCCTGTAATTCAATACAGAAACCAAAC
AGTCCAATTAATAAATGGAGAAAGAGATTTGAATGAACATTTTTCTAAAGAACATCTCAAG
CTCAAGATTTCCCAGATAACTTTTCTTTCTTCAAAAATCTGCTTCTGTGTTTTCCTCATCTG

TAGGTGGCACAGCATACATCTGATTTCCCAAGCCAGAAACCTCATAGTTATTCTTGACTC

CAGGAAGAAATATTATTGAGTTTTTAAAAACTC Sequence 1041

Sequence 1040

CGACCCGCGTCCGTGCTGAACTGAGCTCAGGTGTTTTTTCTCCAAGCTTTCTAGCAA
GGTTTCTACTTAAAATCACCTGTGTGCAAGCCCAAAGGACATTTCATCTATTCTAAGCAG
AAAGGCTGTTTTGTTCATTACAGTGAGTGCTGTTCATCTCATGGAGTGGGAGGAGCACTA
AACCAGGAGACAGAGGACATGGATTTGGTTTCCAGCTTAACCAGTTAGGACTCTGTCCTC
TGCATTCTGGAACCATGATGCCTGCCTGCCTGCCTCACAGGGCTGTTGTGAGGACCAGAT
GAGATGATGTTCATACTTTTGGAATCTCTAATTTAAAGTCTTAATATTTTGTCTTC
TGAGTGTGAGGGGATAAACCTGGATGTAGACTATTAAGCAGCATAGGAGAAAAGAACAAT
AGAATCTAATGGACTGGGTTTGCAATCTCTCTCTAAATGCACTGCTTCAGACAAAGTGAA
ATCCAAAGGTGTGAAAAAAGTATAGCTGCAAATTGGAAAAATGTGTTTCAAGAGT
Sequence 1042

Sequence 1043

Sequence 1044

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CCCGAAGGCTCTAGCAAGGACCCACCGACCCCAGCCGCGGCCGGACTTTGCCCGGTG TGTGGGGCGAGCGACTGCGTGTCCGCGGACGGACGGAAGATGTTAGCCTTCGCTGC AGGACCGTGGTGAAGCCTCTGGGCTTCCTGAAGCCCTTCTCCTTGATGAAGGCTTCCAGC CCGCTTCAAGGCACACCAGGATGCACTTGCCACGGNTTGCCGTGCCCCCTNTTCAGCAGT CCCT

Sequence 1045

Sequence 1046

ACCACGCGTCCGCCCACGCGTCCGGGCGGGGGCATGACTACTGACCCATGCGGGGCAGC
GTCCCTGTGACCTGGCCGATGAGGAAGTACTGAGCCTGTTGAGGAACTGGCCCGGAAAC
AGGAGGACCTTCGGAACCAAAAGAAGCTTCCCAGAGCCGGGGCCAGAGCCCCAAGCGCC
CTCTAGCAGCAAACACAGAAGGAGCTCTGTGTGTCGTCTGAGCAGTCGCGAGAAGATTTC
CCTCCAGGACTTGTCCAAGGAGCCCGGCCTGGTGGGGCTGGGGGCCCCCCATCCAGGA
CGAGGATGAGGGGGAAGAAGGTCCCACCGAACCACCCCTGCAGAACCCTCAA
TGGCGTCTCCTCCCGCCGCACCCCAGCCCTAAGAGTCCCGTGCAGCTTGAAGAGGCCCC
CTTCTCCAGGCGCTTTGGCCTCCTGAAGACAGGGAGTTCTGGTGCCCTGGGTCCCCTGA
AAGGCGGACAGCGGAGGGAGCCCCTGGGGCTTGCAACGCTCGGCTTTCTTCTCCT
GGCTGGAAGGGACCTTCACTTANGCCAAGGAGCTTCGTNTTGGCAGAATTACCCCGACCC
CCTTCCCGAAGCTTGCCGGAGCCCTTNTGTCCTTGTCTGAGGGTCACCAAGCCTTCTTCC
TTTGCTTGGGAGAAACTTCCTTGNCTTNCCTTCAGGAATTCCNGAGCCTGGATTCCCAGCG
AANCCNAACGTTCCCACAGGCTTTCACGGGGC

Sequence 1047

Sequence 1048

Sequence 1049

NCCACGCGTCCGCAAGGCGCTACGTTTATTGCCTCGTCTTATTCACTGACCTTTGTAATG ATACACAGTGAATTCTTTTTGACAAAGAGAAATGCAGTGTAGTATGCAGAGCTGCTGTTT TAATGCCTATGCATTTACTCTTTCCTGATTTAGGCAGAGGTGGCATTTCTTTATTGCAT TTCTCTATTTTTTAATGTACCCTACCTTCAGTATTCTCTTTGTAAGTTGGTGACTTGCA TCTGTGGCCTTGAATATTTTATTATCACATGTGGCATAACAGTATCCACACTTTTTAGTT

TABLE 1 170/467

CTTTATTTTTTTTTTTTTTTTGAGCAATTCTCCTGCCTCAGCCTCCCAAATAGCTGGG ATTACAGGGTGCATGCCACCCCAGCTAATT

Sequence 1050

Sequence 1051

GACCCGCGTCCGGGAGGTTGAACGTTCAGGCTAAGACCGTTACTGAATTGGTTACTAAG
AAGAAGCCAAAGGCTGAAGGCTATGCTGAGGGTGACCTCACTCTCTATCACCGTACCTCA
GTCACTGACTTCCTCCGAGCTGCCAACCCTGTTGACTTCCTCTCCAAGGCCAGCGAAATC
ATGGTAGATGATGAAGAGTTGGCACAGCATCCAGCTACCACTGAGGACATACGGGTGTGC
TGTCAGGACATCAGAGTGTTGGGGCGCAAGGAGCTCAGGTCGCTACTAAACTGGAGAACA
AAACTTCGGCGATATGTGGCCAAGAAGCTGAAAGAACAAGCAAAGGCACTGGACATCAGC
CTCAGCTCTGGAGAGGAAGATGAAGGTGATGAGGAGGACCTCAACAGCTGGAACCACAAAG
CAGCCCTCTAAGGAGGAGGAGGAAGAGGAGGAGGAACAACTGAACCAGACCTTGGCA
GAAATGAAGGCCCAGGANGTGGCGGAATTGAAGAGGA

Sequence 1054

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Sequence 1055

Sequence 1056

Sequence 1057

Sequence 1059

Sequence 1060

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AGTGAAGCAATATGCTGTGCAGTCTCAGCTTCCCGTATATGAGTGGCCGGATGTGGGATC TGGAGAATATGATGTTGGAGTAGTGGCTTCGTTTGGCCGACTTTTGAATGAGGCTCTTAT TCTTAAATTTCCCTATGGCATATTGAATGTTTCATCCCAGTTGCCTCCCGAGATGGCGTG GCCCAGCCCCTGTAATCCATACAGNTGCTTCACGGAGACACAGTTACNTGGAGTAACAAT TTATGCAAATTAGACCTAA

Sequence 1061

GCCGGTTCTTAGGAGGCAGGTGCTGGCCTGGCCTGGATCTTCCCCATGTTCCTGTTGCT GCCTTTTGATACGCCTGATTGTCAACCTTCTGGGCATCTCCCTGACTGTCCTCTTCACCC TCCTTCTCGTTTTCATCATAGTGCCAGCCATTTTTGGAGTCTCCTTTGGTATCCGCAAAC TCTACATGAAAAGTCTGTTAAAAATCTTTGCGTGGGCTACCCTTGAGAATGGAGCGAGGAG CCAAGGAGAAGAACCACCAGCTTTACAAGCCCTACACCAACGGAATCATTGCAAAGGATC CCACTTCACTAGAAGAAGAGATCAAAGAGATTCGTCGAAGTGGTAGTAAGGCTCTGG ACAACACTCCAGAGTTCGAGCTCTCTGACATTTTCTACTTTTGCCGGAAAGGAATGGAGA CCATTATGGATGATGAGGTGACAAAGAGATTCTCAGCAGAAGAACTGGAGTCCTGGAACC TGCTGAGCAGAACCAATT

Sequence 1062

Sequence 1063

Sequence 1064

Sequence 1065

CGCGTCCGAACGGCATCATCACGCCCGCCACCATCCCCAGCCTGGGCCCCTGGGGAGTCC
TGCACTCAAACCCTATGGACTACGCCTGGGGGGCCCAACGGCCTGGATGCCATCACAC
AGCTCCTCAATCAGTTTGAAAACACAGGCCCCCCACCGGCAGATAAAGAGAAAATCCAGG
CCCTCCCCACCGTCCCCGTCACTGAGGAGCACGTAGGCTCCGGGCTCGAACCACCTGTTCC
GCAAGGACGACTACGCGCTGGGTGAGCGTGCGCAGCAGCTGCCCTGCCAACAAAA
GCCTNACGGGACAAGAACACGGCCACGAACCCCCCTGGCCTCACTGGGGTGAGCTTCTTC

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TTCTTGTCGTCATCGTCCTTCTTCAAGCTTGGCCAGCAACGAGAACGCCACAAGGAAACTNGTGAGCCCACGTTNGGCCGTCGGGAAAACACGGGGGN

Sequence 1066

Sequence 1068

Sequence 1069

Sequence 1071

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Sequence 1072

Sequence 1073

CGCGTCCGCTGAGTTCNAGGATGGTTTTTTCTTGGGACCAGACATGAACAAAAGTTGACC
TCATGAGCACTTCAACCTCTCCAGCTGCCATGCTCCTCCGGAGGCTGCGGCGACTCTCCT
GGGGCAGCACTGCTGTCCAGCTCTTCATCCTAACAGTGGTGACAGTTTTGGCCTGCTCGCC
CCCCTGGCCTGTCACCGACTTCTACACTCTTACTTCTATCTGCGCCATTGGCATCTGAAC
CAAATGAGCCAAGAGTTCCTGCAGCAAAGCTTGAAAGAGGGTGAGGCTGCCCTCCACTAT
TTTGAGGAGCTTCCCTCTGCCAATGGCTCAGTGCCCATTGTCTGGCAGGCCACCCCCCGG
CCCTGGCTGGTGATCACCATCATCACTGTGGACAGGCAGCCTG
Sequence 1074

GAGCCGNCCCACGCGTCCNCGGNCGCGTGGGCTACCTTGGAAGCAGTCATCTCTCAGTCT
TACATTTGGAGAATGTGGATGGCATGACATCAGAATTCCTTTATATAATTTAACTTCAGA
ATAGTCTGAGATCATCGAAGCACGATGGTCAAGGGAATTCCGTTTTTGTTTTAGAGCAAA
TATGTTTGCTGTTTGTCTTTCATCACAAACATCAGTGGAGTTTCAGCACCTTACAGAGCT
CAGTGAACCCCCTGGTCACCATCAAAGTTAGCACCAACAAAGCCAACCACGTGTCCCCC
TCACAGATGACAATGGCTGAACTCTGAGTGAAACCACCTGTATGGCCGGGCACAGTGGCT
CA

Sequence 1076

GCCCGCGTCCGCTTTTTGAGAATCTCTGCTCTGTTCCTAGGTTCAGTGCTGGGTCCTGG GAATACAGCAGGACAGACCTCAGCTTATCTCTTCATAGAAATTATACAAAGAGAATTGGG GAGACAGCTAAGAAGAAAACAAAGAAATAAAGCAGTTACAAATTGTGATAAAGTGCTTTT GAAGGAAAGAAGGGGTCTGAGACAACAACAGGGAAGGGGCCTCTCTTGAAACAGTAGTTG GGAAGGAGCAGACATGCACCAGTGATGTGGTGACAGGTGCTCTGAAGGAGGTCACCAGG ACCTGACCTCTTTGAAGGATCAGAAAATACTTCCCTGAAGGACTGACATTTGAGCCTAGA CCTGAAGGGTGAGCCATCAAGCTAAGACAATTGGGGAAGAGCATTCCANGGAGAGGAG Sequence 1077

CGCGTCCGATCTTTGTCTGCTTTCCTATAACTCAGTACTGTAACTCAGTACTCTGAAATA

TABLE 1 175/467

GTTTCCTTTGTTAATAGAGTCACTTTTATAGTACTGNGCTTGAGGNNATATACAGAGTAT TGTGTCCAAATTTATCATTGCACAAAGTGTTTTTGGAAATTCTTGGTTACTCCTTAGTAA ATTACCTGTAATTGGGTTAAATGCTGGTAGGGTTTAAAATCTGATTGCTAAAGTGAATTC TCTATAAAGTGAGTTTTGATACATAGAAACTTTNCATATAATTCTTAAACTCATGTGCA TGTATTTTCATTTTTCATATTCATTAACATATGTTGTTCCTTACCATTTACAG CTCANAATTCTGCANATGCAGATTTTTGCAAACTTTTGATGCATTTGGACAGTCTAGTGGT TCGAGTAATTTTGGAGGGTTT

Sequence 1078

TNCGGGCGGCTGCGGCGGCGGCAGGCGGCAGGCCGGCAGGCGGTGCGCGGAGGGCT GGTACCCTNAGCAGGTGGGCGGGGTGCGGTTGGNGGCGGCGGGCCGGGGGCTGCC CGGCTGCGCTCGGGCCGTGCGCGGNGGCCGTGCGGGCCACGCCATGGACTTCAACATGAAG AAGCTGGCCGTCGGACNGCGGGCATCTNTNTTCACCCGGGCCGGTGCANTTCACGGAGGA GAAATTTGGCCAGGCTGAGAAGACTTGAGCTTGATGCCCACTTTGAAAACCCTTCTGGCC CGGGCAGACAGCACCAAGAACTGGACAAGAAGAAGATCTTGAGGCAAGACAAGAGGTGCC TGCTGCAGCCCCAACCCCAGTGCCCCGAGTGGAGGGAATTANCTGTATGAAGAAGCTTG Sequence 1079

Sequence 1080

Sequence 1082



NNTGGGNTTTTGGTCCCAAAACCTCATCNAATGGGTANTCTTAATCATGTCCTNGGGATCCCCCCGGGTTACCCGGAGCCTTCGGAAATTAAATTTCCTTCTTTCCGCTTTTCCTTCGCTTCACTTGACCTCCGCTTNGNCTCGGGGTCCGTTTCCGGGCTTG

Sequence 1084

CGCGTCCGGACTGTCGCTCTAAAAGAATGAAGGAAATAATAAAGTGATAGACAGGGAAGG
ATAGAAAAGACTTAACAATATACATATGTTCCGTCTTTGCTGTTTTTGGAGAATGATGGAT
AAGTANGTGTTTCCTGATTCTGAAGCATAGCTGAACAATTTAATTGTGGTTTACCATCTT
TTTGGTTCCCTCTCAGTAATTAACCTATCGAAAATCTGTCCTAAATGTTTGGACTGGGG
CACAGTTCCCTCCATCGCTTTGGGAGAAAATCATTAATATGGCATACTGCAGATTTGCAG
GCAGGACCACTGAGGGTGTCATAGACATTAGCTCTATGGAATTCTGCTAGCAATTTCCAA
GTGACAGTGAGGAATTATGGATATATGTTTGAGGTCATTCAAGCTTCCTGAGTACCACAT
TCCCCAGCTACTTAGACACCGGGTTAAAAATATTAAAGATGTCCTAGTTCAACAGCTTGAA
TTCCATTGATTGGAT

Sequence 1085

GACCCGCGTCCGGCTTCCTGGGTTCGAAAGAACCCAGTTCAGGAGTTTCTGTTTTAGTT
TGAGATCTTATAGGCCTGTCTCATCAGGTTGGTGTCAGCCCAGCTAGGATTAGGCAGAAT
TGGGTGGGGGCTGTAGTGCATCTTTGGCACAGCATGTACCTGTCTGACTAATTCTCTGTC
TTTTCTTTCCTGTTGCAATTCATGGGTCTTAGCATCTTCTGAATGGTGTTTAGTAGGTCA
TCCTGTTGATTTCCTGCTAGGGAGTAGCATACTCTGGCTCTGTACCATTGGCCAAGGGAC
TTAAGGATAGGTGAAGGGCTGCAGTTTTGTTAAATGGAACAATATGAAGAGATGGCATTG
TAAAAAAAACTTNTGNCAACTNAA

Sequence 1086

Sequence 1087

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Sequence 1088

Sequence 1089

Sequence 1090

CGCGCCTGGTAAAATTATATAAGCTTAAAAAAAACAAAAACAAAAACACTTGCTTTGAAAA GAGTCTCTCAGCAGCAATTTTGTCCTTGCCCCCTACTTCCACAGTTCCTTTTCTTACCATT TCACATCTGGATTACTACATTGGCCTCTTTGCTTAGACTCCCAATATTCATTTGCTTTCC TTCACCCCATTTTATGGAGGACTGTCAGATCAATCTTTTAAAGATAAATTTTATAATGTT ACTACTGTTGCCTATTGGATTAGAGCCCTAGGGGTGCTTTTTGTAGTCTCACTGACAGCT GACATTAGTGATTTTCACCCTCTTCTTATTGCTACCCTGTTTGATGGCCAGTTTCCAG GTGGGCACCTGCTCCACTTGCTTTCAT

Sequence 1091

GGGGTATGTGTGTTCTCCAGGAAAGTGCTGAAAATATCACCCAGGCCTCTGCGCCACG
CCCTGGGAGAGTACACTCCTGGGCTCACGCCTCTGCATTCCAAGGCTGACAGCTAGAAAT
ATACTTTGTAAAATACCAACAACTTATTCACAAATATTCCAACTATCTACCAGCTCCAAT
GAGCTTGCTGAGGATGGGTATGACCCCAGTCTAAGGGGAAAGAATCTAAAACACAAGTAA
ACCTGTTTAAAGGCCAGATCTCCAGATGGAGATCCAAGCAGATGGCGCCTAAGGTTTGCC
CTTGAAAACTACCAAGGAAGCCACAGAGAGGGGATCTTTGGACCTTCTGGAAAATGGTAAG
GCCCCAGGTAGATTATGGCTCCTCTGCCCTGGAGGCTGAGCCGCCCTCTGGTTACCTCAC
ATCTTCTGGTTTCTTCTGAGTGGGACTTGATCTCATTTCTGCATTCACAGCAAGGNGGAA
CTGTCTGGCAAGAGCTTAAAATTAGGACCTGNTGGTGGGGACCTTTAATAGCAGGTGGAG
GGTTTGAGATCCCNTGAGATGCCCNAGATTAATTCAATAGGGGGANGAAAGATTTGGCCC
AATTCAAAAGNGCTTAAAAAAAAAATTTT

Sequence 1092

Sequence 1093

CGCCCGCGTCCGATAAAACTGGATTTGATTTCTTTTTATGAAANGTTTCATATGAATGT
AACTTGATTTTTACTATTATAATCTAGATAATATGATATAAAGAGGGCTAAGAATTTTA
AATTGAATCATATATATGATATAATTTGATCCTTCTTGTATCTTGAAGTTTTGTACTTGG
GATTTCTGGACTGATAAATGAATCATCACATTCTTCTGGTAAATATTTTCTTGGAGCTCT
GTGTCAACTTTGATCCTTTGTCTCCCAGGAAGGTGTGACCTCTCCTTTGCCTGCATACCT
CAAGGCCAGGGGAATATGCCTCAGTGATGCATTTATCTTTGTATATCAGGCCGCATGATT
CCCAACTTTCTGCCACACTTAAATTACGTTCCTCCATTTCAGTTTTGTCTTTTCTGTCTA

TABLE 1 178/467

AAGTTCAGTCAAAGAGTATCAAAAAATTATGTTTCAGCTAGACTGGTGTAATGTATAAGTTTTTGTATCTTGTATTAGAGGATTTCGTAGCTTTTATTAGAGG

Sequence 1094

GCCCGCGTCCGATCCCTAGATGACATAACAGCCTTACAAAAGGACAGGGAGGAGTGTCT
GTTCCTACTCTCACATAGCGGAGGAAAGTTAGAGCCTCTCAGTCTCTGTTTATGAGGACT
CATTAATCTCAAATAATTGATGCATTTTTCATACATTAGGGTCTCTGTCCATGTGTCTTC
CTGATATTGTTATAGAAATGGCTTCAGGCTGCTGGTAACAGATGCTGCGGAAAAAGAATG
CCTTAAACAAAGCCAGGCGCGGTGACTCACGCCTGTGATCCCAGCACTTTGGGAGGCTGG
GGTGGGAAGGATCACTTGAGCCTAGGAGTTAGACACCTACCCAGCCTGGGCAACACGGTG
AGACCTCGTCTCTACAAGAAACAAATAATTGGCTAGATGTCGTGGCGCACAAGCTTGTGG
TCTCGGCTACTTAGGGGGGCTGAGGCGGAGGATTATTTTGAGCCTGGGGAGGTCAAAACTG
CGGTGGGCTGGGATTGCGCTACTGCACTCCGGGCTGGGAGACCGAGTANGACCCTGCCTT
AAAAAAAAAAAAAAAAAAAAAA

Sequence 1095

Sequence 1096

GTNGCCCCGCGTCCGAGTNAACAGTGGTAGTNAAATTCAGGGTTGGTAAGTTTTTCCATA GAAGGCCAGATGGTAAATATTGTAGGCTTGCAGACCATGTGGGCTCCACGACTCAACTCT GCCACAGTAGTTTGAAAGCAGCCACAAACAGCCTTGGTGTGACTTTGTTCCAGTAAACTT TCTTTATAGAATGGGAGAAAATATTTGCAAACAATGCATTCAACAATGGCCTGATGTCCA GAATTCATGAGGAACTTAAAAAACTCAACAACAAAAAATCACCAAATAACATTTAAAAGTG GGCAAAAGATATGAATAGTCATTTTTCAAAAGAAGAACATACCGAATGGCCAACAAGCATA TGAAAAAATACTCAACATCTCTAGGCTTTCAGAGGCATGCNAANTAAAACCNCCATTNGA TATTATNTTACNNGANCCCNAAATGGGTTTTTTTTAAAAGGCCAAA Sequence 1097

Sequence 1098

TABLE 1 179/467

AATTCTATTAAATGGTGTAAATGATGAAATTATAGTTGATATATGCTAGAGCATCAGTGC TGGGTATTTTAGAAGGGATGGA

Sequence 1099

CGGGCCTGTTCCTAGAGCCTCATTGGAGACATTGACAATGCCATGAGGACCTTCCTCAAC
TACTACACTGTATGGAAGCAGTTTGGGGGGGCTCCCGGAATTCTACAACATTCCTCAGGGA
TACACAGTGGAGAAGCGAGAGGGCTACCCACTTCGGCCAGAACTTATTGAAAGCGCAATG
TACCTCTACCGTGCCACGGGGGATCCCACCCTCCTAGAACTCGGAAGAGATGCTGTGGAA
TCCATTGAAAAAATCAGCAAGGTGGAGTGCGGATTTGCAACAAAAGATCGCTTTGGCTGC
TTTGTGAAGAATAGATTGAAAGGGTCAAAGGTGAGAGCCATCTCACATCCATGCAGGAAC
CAAGCAGGCAAGATATAAATATGAAAGTAGAAGAAAATAGTCTGGAAGAAAAATCCC
Sequence 1100

Sequence 1101

Sequence 1102

Sequence 1103

Sequence 1104

TGCCNCGCGTCCGAGCATCTCAGGTAACAATTTGAGCATAACTTTAACCATAACTTATGA TAGCATAATAACATTCATTAGTAATTCAGTAGCCGTATGTGCCAGGCTGTGTTAGGTGCT TTATATATTGTTTAATTTTTAAAAACTTGTGGAGTGTACAGATTGGTAAGGTGACATTGT ATCACAAAGCTAGTCTTTGAGTCCAAAGTTTTGTGGTTTTATGTTATGATATACTTTTAT

TABLE 1 180/467

Sequence 1105

Sequence 1106

Sequence 1107

Sequence 1108

CCGTCTCTGGCTTGGCCAGGTTTAAATTAATAAAAATGAAGATGAAAATAAGTTGTCAGA TTTAGGATGTATTTTAGAAACCCAACTGATAATTTGCCAACTAATTGGATGCAGAGAGTA AGAGGGAGACTCAAGAACACCTCTAAGATTTTTACCCTGATCAATGGGATAGGTGAAAGT ACATTAATGGAGATTGAGAATCCTGGTGGAGGTACAAGTTTAGGGGTACTGAAGAGTGCT TTTGGACATGTGAATTCTTAGAAGCCTACTAGATTCTCCAAATGGAGACATAAAACATAA TTGAATACAAAAGTCAGGAGTTCAGGAGAGGGCTGAGCTAAAGATACAAATTTGATAGAC ATGAGCATTTAAAAAAAACTGCATGAAAATACTAAAGATAGGCTGTCCTGCCTATGGAAT

TABLE 1 181/467

AGCCATTCTTTGATCCCTTTACTTTCTTAATAAACTTGGTTTCACCTTACTCTATGGACT TCCCCCAAATTCTTTCTTGTGTGAGGTCCAAAAACTCTCTGTTGGGGTCTAGATCAGACC CTTTTCAAGTACATCTTNCTGATGAACCACAAANGGATTATACTAAAGAGACCCCCCACC

Sequence 1110

Sequence 1111

CCCACGCGTCCGCGGCCATTTCTGTATCCCCCTGCCTGGGTTTGCTGCCCTTTATGCTCC
TACCTCACCAGGTACAAGGAACATGAAGATGGCTATATGCGGCTGCAGCTGGTTCGCTAC
GAGAGTGTAGAGCTGACACAGCAACTGCTGCGGCAACCACAAGAGGGATCGGGCCTGGGA
ACGTCGCTGAACGAGAGCAGCCTGCAGGGCATTATTCTAGAAACAGTGCCAGGGGAGCCA
GGACGTAAGGAAGAGGAAGAGGGCAAGGGTAGCGAAGGGACAGCCCTCTCAGCCTCT
CAGGACAACCCCAGTTCTGTCATCCACGTGGTGAATCAGACCAATGCCCAAGGCCAGCAA
GAGATTGTCTACTATGTGCTGTCTGAAGCCCCAGGGGAGCCTCCCCCAGCCCCTGAGCCA
CCTTCAGGGGGCATCATGGAAAAGCTTCAAGGAATAGCTGAGGAGCCAGAGATCCAGATG
GTTTGAAGGCCGCAGAGCCAGACCATTTCTTCCCAGGTCTGAAAGTTTGAGCCAGGCAAG
TGGCAGTGCCCTAGTGGGCAGCCGTTGCCAATGGATGCC

Sequence 1112

TCGACCCCGCGTCCGGTTTTTTGTCCCAGCAGTGGCATTTAAATTACTGTACTTTAAGAC
ATGGAATTGCTGGAGGCTTGGAAACTTGAGTGCAATTTCCCTAGTACGACCTCCAAGGAG
AATAGAGCAAAACAGTGGTAGGAAAAACTCTCAAAATTTTACCCAATTGTATGTTTTCTA
CATTGTCAGTATCTAGTTTATATAGTTAATATGTACTTCTAAAATTTCTGACAGTGNTT
GGTGTATAAAACAGACCAAGCTCAAGATGTAAAGAAGATTGAGAAATTCCACANTCAACT
AATGCGACTTATGGTAGCCAAGGAAGCCCGCAATGTTACCATGGAAACTGAGTGAATGGT
TTGAAATGAAGACTTTGTCGTGTACTTAGGAAGTAAATATCTTTTGAATTAGAGAAAGTG
TTGGGACAGAAAGTACTTTATGTAACTAAGTGGGCTGTTCAGAAGCTTAGAGGTCATTTT
TTGTAATTTTNTTTTTAATTACTTTTAGAAGAGCCTAGGGATGCAAATGTTTTCAATTTGGA
AAGCCTTTATTTACTTTTTGGAAA

Sequence 1114

TCGACCCCGCGTCCGATTCCTTCTTCATATATTATGTCAGAAGAGTTTGAGAAGAAATGG
TATTAATTCTTCTTTAAATGTTAGGTTGACTCACCAGTTAATGCAGCTATTTGGTCATAA
ATGTTTCTTTGTTAATCACTTTCGATTACTAATTCAATCTGCTAGGTTATAGGTCTATTC
AGATTTTCTTCTTCTTGAGCCACTTTGGTAGTTTGTTCACAGTATACTCCTGTAATCC
TTTCATCCAGGACAGCTAATTTGTTTAGACAGTTGTTCACAGTATACTCCTGTAATCC

TABLE 1 182/467

Sequence 1116

Sequence 1117.

Sequence 1118

GCGTCCGTTGTCATCTATTTACTTTACATATGTCATAAACCTAACACTACATGGTCATTT
TTGTTTAAACAGTCAATTACCTTTTAAAGGGATTTGAATAATAAGTCAAAATCTAATACA
TTAACTGTGTAGTTAGCATTTCTGGTGCTCTTTCTTTTCTGTAGATCCATACTTCCA
TCTGGCATTATTTTCCTACTGCCAGAAGGACTTCCTTTAACATTTCTTGTAGTGTAGATC
TGCTGGTGATGAATTCTTTCAGCTTTTGTAATTCTTTTGAAAGGTATTTTCCCT
GAGTATAGGTTAATAGCTTTTTCCTTTCAGTACTCTAAAGATGTTGCTCCAGGCCAGGCG
CGGTGGCTCACTCCTGTAATCCCAGCACTTTGGGAGTCTTGAGGTGGGCAGAACACTTGA
GGTCAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCCCGTGCTTCTAAACATAT
TAAAGAAAAAAAGA

Sequence 1119

NCGTGACATGCTGGCTGCTAGTNAGCTCCCCCATGATTGTCAGCTTCCGAGCCCTCACTAGAAGCAGATACCACCCCCACCACCATGTTTCCTTTAAAGCCTGCAGAACTGNGAACCAATT

TABLE 1 183/467

Sequence 1121

CGGCCGAGGTACTATAATGGTCCCCATCTTAATTTGAAAGCGTTTGAGAATCTTTTAGGA
CANGCACTGACGAAGGCACTNGAAGACTCCAGCTTCCTGAAAAGAAGTGGCAGGGACAGT
GGCTACGGTGACATCTGGTGTCCTGAACGTGGAGAATTTCTTGCTCCTCCAAGGCACCAT
AAGAGAGAAGATTCCTTTGAAAGCTTGGACTCTTTGGGCTCGAGGTCATTGACAAGCTGC
TCCTCTGATATCACGTTGAGAGGGGGGGGGTGAAGGTTTTGAAAGTGACACAGATTCGGAA
TTTACATTCAAGATGCAGGATTATAATAAAGATGATATGTCCGTATCGAAGGATTTCGGC
TGTTGAGCCAAAGACTGCGTTACCCTTCAATCGTTTTTTACCCAACAAAAGTAGACAGCC
ATCCTATGTACCTGCCCG

Sequence 1122

CCCTTCGAGCGGCCNTNCGGGCTTNTACGCGGGGGCAGCGGGAAGCTCGCAGCAGCTGGGAGGAGCCAAAGCCTCGGCGCTCACCTAAGCCGCAGGGAGATACACCCAACTGGGAGAT GAGGAAACAGCAACCCAGAGAGAGAACTAACCCACACAGGATCATTTCGCGAAGGAGCA AGGCTGAAGAACCTGGACTTTCTTAGGACAAACTTACTGCAGCTTGAAGGAGCCA ACCATGGATTTGAGGCGTGTGAAGGAATATTTCTCCTGGCTCTACTATCAATACCAAATC ATTAGCTGCTGTGTTTTAGAGCCCTGGGAGCGATCTATGTTTAACACCATCTTACTA ACCATTATTGCTATGGTGGTATACACTGCCTATGTCTTATTCCAATCCACATTCGCCTG GCTTGGGAATTTTTCTCAAAAATAT

Sequence 1123

Sequence 1124

TABLE 1 184/467

NATGTGGTGCCCACTAGGCTACTGNTGAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTA TTCAAAATATGTAATGACTGGTATGGCAAAAGATTGGACTA

Sequence 1125

Sequence 1126

Sequence 1127

Sequence 1129

TABLE 1 185/467

CACTAGGCTACTGCAAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTATTCAAAATATG
TAATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTGGACAGGGTTA
TGTTAACACCTGAATTGCTGGGTCTTGAAGAGAGGCCCAAGGAGTTCTGGGAAGAGGGACC
AGATTGGGGGGTAGGGTCACGGGCTTGGGTGATAGAATTATTTCTCGAATGACTTTCTTG
AGTGCCAATTTGAACTGTAACATTTGCTTANTCACCTTTAGNGGAGTAATCTCCTGGGCT
TGGTTCTATATTTATATAAAAAG

Sequence 1130

CGGGCAGGTACAGCCTCTCGGCCCGGCTAAACATCATCGTCTTGGTAGGCCATTACCCTA
CCAACTAACTAATGTTCCGCACCCCCATTTTTAAGTGAAGCTGTGAAGCTCCTTTCTATT
ACTCATCATGCGATAAATAACTATATCCGGTATTAGCTATTGGTTCCAATAAGTTATCCC
CAGTCTTAAANGTAGGTTAAGTACCTCNGGCCGGCCACCGGGNTGGAGCTCCAAATTNGC
CCTATAAGTGAGGTCGGATTTACGCCCGCCTCACTTGGCCCGNNGTTTTACAACCGTCC
GTNGACTNGGGAAAACCCCTGGGCGTTTACCCCCAANCTTTAATCCGCCTTGGCAGCACAA
TCCCCCTTTTCGNCCAGGTTGGCGTNAATAANCGAAAAAGGCCCGGAACCGAATCGGCCC
NTTTCCNAACANGTTNGCGCCAGTNCTGGAATNGGCNAAATGGGGACCCCNCCCCTTGTT
AACCGGGGNGCATTTAAACCNCCGGCCGGNTGNTGGTTGGNTTACCCCCCAANNGGTGAC
CCGNNTTCAACTTTGGCAAGGGCCCCTAANGGCCGNTTTCTTTTGNTTTTTTC
Sequence 1131

Sequence 1133

CCCGGGAACAAAGCNGCAACCGNGCCCCCCCCCCCAGGTCNACGGNNTCGANAAGCNCGA AAACCGAATTTTTGNAGNTTTNGGGGACCCACTANTTNGNGAGCGGGGGCCGANNNAGNG CGGC

Sequence 1134

TABLE 1 186/467

GAANCAGAAGAAGGGGCGCCCACNAGGCTACNGCNGAAAGGGAACCGAAAAACCCCNCA CCAANNAGGNATNCAAAAAANNGGAAACGGACCGGGNCANGGCAAAAAAAANGGAACCAA GACACCGGGCCCANACCACNGGACCANGGGGNAANGGAAACACCCCGGAAATGGCAGGGN CCCCGAANAGAACCCCAAGGGAGCCCAGGGAAGAGGGACCCAAGATGGGGGGGAAAGGC CCACCGGGCCNGGGGNGAAANAACAAAGCCACCGAGGGCCAACCGNAAGNGGCCAANNGA ACCCGGAACNANAAGGCNNAANCCACCCTGAAGNGGGAGAAAACCCCCAGGGCNGGGGG CCAAANANNAAAAAAAAGCNGCCCAAAACCCCCAA

Sequence 1136

NTTTAATTTTTTGCAGCCCGGGGGANCCAGGGGNAGGGNGAGCCCACCGCGGGGGAGCGCCAANCGCCCNACAGCGAGNCGNAANACGCGCNGCCCACNGGCCCGCGNANAAACAACGNCGAGACGGGGAAAACCCCGGCGNCACCCAACNGAAACNGCCANGCAGCACAANCCNCAANCGCCAGCGGGGGGAANAGCGAAGAGGCCNCGCACCGAACGCCCANCCCAACAGNGGCGCAACAGAAAGGGCGAAA

Sequence 1137

Sequence 1138

TTACCCCGCGTCCGGGTAAACAAAACAAAGATCGTTTGTTCTGGAAACAGGTAAAATGGT
AATCAAATAGATTGTGTTCCAGGAGTGCAAAGGTGGCTTAATATTCACAAATCAGTTGCT
ATTGTACACCACCTGTAGAAAAGTAATCTGGCATGCAGAACATTCTTATGGTAAAGTTAA
TGTTCATTTATGATCTTAGCAAATGATGGATTGAAAGGGACTTCCTTAATTGCATAAACA
GACTTCAACAAACAGTATGATGAAATAGTGAACATTTCTCCCTAAGATTATAAAAATAAGA
CAAGGATATCTGCTGTCAATGATTTTATTCAGCATTGTTCAGAAGGACCTAACCAGAAAA
CTAATGCAAGAAACAGAAACAAAAGGCATAAAAGATTANAAAAGAAGTAAAATTTTAAAAA
AGAAAAAGAATATAAATCTCTATTTGCATATGCCATGAGTAAAATTTGGTAAGTTCCCTGC
ATAAAAGTTATGCAAAAAAGCATTTTTTTGATATACCAGCCAAAAATCAAGGGAAATGGAA
AA

Sequence 1140

TABLE 1 187/467

AAGCAGATGAAGACTCTGAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAA GCTGGAATGGGGAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAG CTGAAATTCCTCCACCAAGTTGGTATTCAAAATATGTAATGACTGGTATGGCAAAAGATT GGACTAAGACACTGGCCATACCACTGGACAGGGTTATGTTAACACCTGAATTGCTGGGTC TTGAGAGAGCCCAAGGAGTTCTGGGGAGAGGGACCAGATTGGGGG

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCACTCTATCCATCGTGGATA
GAGAAACTGAAGCTCTCTAAAGACCCTGCAGCTGGGAGGTGGCAGAGTCAATGGCAGCCC
TCAGCCCTATCTGCCCTGACATGGCATTCCTCCCATTTCTCACCACCGAACCCTCTAAAA
TAACAATGTGTGGGGTCCTTGGCTGAGAGACTTNCCTTTTGGGAATCAATCTGAATGTAT
GATGACAAAGAAAACAACTTTTGCTTTATACAACCTTCTGGTTAGATTCAGGCACCAAGC
AGGACACTTCTTTGTGGCGCTCCAAGAATCTTTCAAATTCTTCATCACCAATAACAAATC
TTTCTGCTTCTCTTAGAGCATCTTCTCCACAATTCTCACCTCAATTAAGAGGCACTGGA
ACACTTTCCAGCGGACAGGGTTTAGTGCTTTGATCTGTTCCGTCATGTCCTCTCCACGT
TGAAACGATTAATGACAGAATTTTTTTTTGGAGGCGACTCTATTAATCCCTACACCACCTN
CTCAGCTTTTGAAGGGTTTNCACATGGGTTCTTTT

Sequence 1144

Sequence 1145

TABLE 1 188/467

ATGGGGAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGC Sequence 1146

Sequence 1148

Sequence 1147

TTAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCCCCGGGCAGGTACGCGGGGAGTTCT GCGCAGCTTCCCGAGGCTCCGCACCAGCCGCGCTTCTGTCCGCCTGCAGGGCATTCCAGA AAGATGAGGATATTTGCTGTCTTTATATTCATGACCTACTGGCATTTGCTGAACGCATTT ACTGTCACGGTTCCCAAGGACCTATATGTGGTAGAGTATGGTAGCAATATGACAATTGAA TGCAAATTCCCAGTAGAAAAACAATTAGACCTGGCTGCACTAATTGTCTATTGGGAAATG GAGGATAAGAACATTATTCAATTTGTGCATGGAGAGGAAGACCTGAAGGTTCAGCATAGT AGCTACAGACAGAGGGCCCGGCTGTTGAAGGACCAGCTCTCCCTGGGAAATGCTGCACTT CAGATCACAAGATGTGAAATTGCAGGATGCAGGGGGTGTACCTTGGCCCGCTCTAGAACT

Sequence 1149

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCAAATGAAGTG
TGAAGACAAGGCCATCCACCACTTTATAGAGGGTGTAAAAATAAACCAGAAATCAAGGGA
NAAAGAAAAGATGAANGACAAACTGCAAAAAATTGCCAAAATGCNACTTTCTAAAAATGG
AGCAGATTCTGAGGCTTTGCATGTCTTGGCATTCCTTCAGGAGCTGAATTGAAAAAA
Sequence 1151

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Sequence 1152

Sequence 1153

Sequence 1154

Sequence 1155

Sequence 1156

CCGCGGTGGCGCCCCGGGCAGGTACATTGGCACGTCACGATGTCTTGAGTTTCATTC
ACTAGGTGGCAGCCTGCATCGTTCCACTGCAAATGACTGAAATCCCAAAACACACAATGA
GGCTGGCTCAGGTTTGACTCTATCTTGGAAAAAAATAGGAAAACTTCATTTATGGAATAG
TTTTGAATAACCGTGGATATCACAGGTCCATTGACCTGAGCATTTCCATTTTTTGGAAACG
GGTAGAATGTTCCCCAGAGTCAACGAGGCCATGCTGATAATAGTTTCTGGAAGGGATCTC
TGGAATTGGTCTGACCCAATTAACACACGGCCTCTGATGGGAATAGATGTATTTTGGGGA
CACATTTTAATCTGATAGCTGTAACCCCTTTTGAGTTGGCTTTTTTTCACTGGAATCCCT
TTCCAGTCAATGAATTTCCGAGAAAAATTCAGAGGAAGAGCTGTCGGAGGCACCAGAGTG
CTGATGTTTTCT

Sequence 1157

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TABLE 1 190/467

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGCGGGCAGTGGGA
AGCTCGCAGCAGCTGGGGAGGAGCCAAAGCCTCGCGCGCTCACCTAAGCCGCAGGAGATA
CACCCAACTGGGAGATGAGGAAACAGCAACCCAGAGGAGAACTAACCCACACAGGATC
ATTTCGTGAAGGAGCAAGGCTGAAGAACCAGACCTGGACTTTCTTAGGACAAACTTACTG
CAGCTTGAAGGAGCCAACCATGGATTTGAGGCGTGTAAAGGAATATTTCTCCTGGCTCTA
CTATCAATACCAAATCATTAGCTGCTGTGTTTTTAGAGCCCTGGGAGCCGATCTATGT
TTAACACCATCTTACTAACCATTATTGCT

Sequence 1159

GGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACGCGGGCAGTGGGAA
GCTCGCAGCAGCTGGGAGGAGCCAAAGCCTCGCGCTCACCTAAGCCGCAGGAGATAC
ACCCAACTGGGAGATGAGGAAACAGCAACCCAGAGAGGAGAACTAACCCACACAGGATCA
TTTCGTGAAGGAGCAAGGCTGAAGAACCAGACCTGGACTTTCTTAGGACAAACTTACTGC
AGCTTGAAGGAGCCAACCATGGATTTGAGGCGTGTGAAGGAATATTTCTCCTGGCTCTAC
TATCAATACCAAATCATTAGCTGCTGTGTTTTTAGAGCCCTGGGAGCGATCTATGTTT
AACACCATCTTACTAACCATTATTGCTATGGGTGGTATACACTGCCTATGTCTTTATTCC
AATCCACATTCGCCTGGCTTGGGAATTTTTCTCA

Sequence 1160

Sequence 1161

ACTTAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGCCGGAAGGTGGGTGACGTGCGGA TCTTCTTCTTTTTGTGGCTGTGGACACCTTTCAACACTGCCTTCTTGGCCTTTAAAGCCT TCGCTTTGGCTTCAGCTTTAGGAGGGGCAGGAGCCCATCGCAAAACCACGCTGCGGAGAG AGGGGCGGGTAATGTAGCCCGGTTGAACATGAACCAGAAGGAAAATGGTTAAAGCTGAGG GCACTAATTCCTTACAGGCCCGGGGACATGGAGCTCCAACCAGTGGATGCATGTAGCTTC CCAGAACCGAATGTCTGCCCCGCGTACCT

Sequence 1162

CCGCGGTGGCGGCCGAGGTACCACTCTATCCATCGNGGATAGAGAAACTGAAGCTCTCTA
AAGACCCTGCANCTGGGAGGTGGCAGAGTCAATGGCAGCCCTCAGCCCTATCTGCCCTGA
CATGGCATTCCTCCCATTTCTCACCACCGAACCCTCTAAAATAACAATGTGTGGGGTCCT
TGGCTGAGAGACTTCCCTTTTGGGAATCAATCTGAATGTATGATGACAAAGAAAACAACT
TTTGCTTTATACAACCTTNTGGTTAGATTCAGGCACCAAGCAGGACACTTCTTTGTGGCG
CTCCAAGAATCTTTCAAATTCTTCATCACCAATAACAAATCTTTCTGCTTCTCTTAGAGC
ATCTTCTCCACCAATTCTCACCCTCAATTAAGAGGCACTGGAACACTTTCCAGCGGACAGG
GTTTAGT

Sequence 1163

TABLE 1 191/467

AGATGAAGACTCTGAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAAGCTGGAATGGGGAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTATTCAAAATATGTAATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTGGACAGGGTTATGTTAACACCT

Sequence 1165

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCATTTTCTTTNTCCTGT CCATAAATCTTCTTCCACCACGTGGCTGTGTNCAAGACTCTCTGAACCTNCTCTGGCTCA GGAGGCTTNTAGATNTGTGAATTGTCTGCTCAGTNNAACTCCATTAAATTNAATNTGGCC AAGAANTTTCTTCTTAACAGNGGTATTGATGACCATTAATCCTTCAACCTAAACCTGCTC ATTAA

Sequence 1166

Sequence 1167

Sequence 1168

TABLE 1 192/467

GAGGGGTTTGGAGTCTGGAAGCCTCATCNCTTCAGCATCAACTGGAATGG

Sequence 1170

Sequence 1171

Sequence 1172

Sequence 1173

AGGTACCGCTGTGTCCGGGTGGTGGTCAGAATGCCGTGCTCCAGGTGTTCACAGCTGCT TCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTACGCAAATGTTGCCTGTGCC CAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAGAGTGAGCTCGCTGGAGGGG CAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTCTTGCCAGATGACAAGGTGACTGCA TTACACCACTCAGTATATGTGAGGGAGGGATGTGCCTCTGGCCACGTGGTTACCTTGCAG TGCACAGCCTGTGGTCATAGAAGGGGCTACAGCTCACGCATCGTGGGAAACATGTCC TTGCTCTCGCAGTGGCCCTGGCAGGCCAGCCTTCAGTTCCAGGGCTACCACCTGTGCGGG GGCTCTGTCATCACGCCCCTGTGGATCGTCACTGCTGCACACTGTTTTATGACTTGTAC CTGCCCG

Sequence 1174

AGGTACCGCTGTGTCCGGGTGGGTGGTCAGAATGCCGTGCTCNAGGTGTTCACAGCTGCT
TCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTACGCAAATGTTGCCTGTGCC
CAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAGAGTGAGCTCGCTGGAGGGG
CAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTCTTGCCAGATGACAAGGTGACTGCA
TTACACCACTCAGTATATGTGAGGGAGGGATGTGCCTCTGGCCACGTGGTTACCTTGCAG
TGCACAGCCTGTGGTCATAGAAGGGGCTACAGCTCACGCATCGTGGGAAACATGTCC
TTGCTCTCGCAGTGGCCCTGGCAGGCCAGCCTTCAGTTCCAGGGCTACCACCTGTGCGGG
GGCTCTGTCATCACGCCCCTGTGGATCGTCACTGCNTGCACACTGTGTTTATGACTTGTA
CCTGCCCG

Sequence 1175

AGGTACCGCTGTGTCCGGGTGGTGGTCAGAATGCCGTGCTNNAGGTGTTCACAGCTGCT TCGTGGAAGACCATGTGCTCCGATGACTGGAAGGGTCACTACGCAAATGTTGCCTGTGCC CAACTGGGTTTCCCAAGCTATGTGAGTTCAGATAACCTCAGAGTGAGCTCGCTGGAGGGG CAGTTCCGGGAGGAGTTTGTGTCCATCGATCACCTCTTGCCAGATGACAAGGTGACTGCA TTACACCACTCAGTATATGTGAGGGAGGGATGTGCCTCTGGCCACGTGGTTACCTTGCAG TGCACAGCCTGTGGTCATAGAAGGGGCTACAGCTCACGCATCGTGGGTAAACATGTCC TTGCTCTCGCAGTGGCCCTGGCAGGCCAGCCTTCAGTTCCAGGGCTACCACCTGTGCGG

TABLE 1 193/467

GGCTCTGTCATCACGCCCCTGTGGATCGTCACTGNTGCACACTGTGTTTATGACTTGTACCTGCCCG

Sequence 1176

Sequence 1177

TAGGGCGAATTGGACTCCACCGCGGTGGCGGCCGCCCGGGCAGGTACCTACGGAAATCCT
AACTACCACTGGCAGGAAACTGCATATNTTCTGGTTTACATGAAGANGGAGGGCTAANGG
AAATGCCCAAAACCTTCAGAGATTGACACCGCTGTCATTNTCCATNTCNGTTCCTGGAAT
CTACCGGGAGTNTTNATAAGAAGANTTTTGCAAATNGAGGGAAGAAGCAATTGTTTTCAA
ACTATATAACTGGAGNCCTTAATTTATAATTAGGGGATATTTAATCAAAAATATNGTAAA
CCATGGAGGGCCCCCTCAGNGTNCTGGATCAGGTTCAAGAAATNGAAATGNTTTTCACCC
AAGNCANGACCCCGGCCATGTGGGCATGNTCCGGGTNCCTGGGGGTGGCNTCGNCTGGCT
TGTGGCGAANGAACAATTAAGCCCCTTTTAAGTTTATTGAAGCCCTGNGGGGAAACTTTA
AGGGGGTTTCCANAGTTGGGGGANGAAGCANTNGGNNAGTTGGNGAAGGGCATTTTGGGG

Sequence 1178

Sequence 1180

CCGCGGTGGCGCCCCGGGCAGGTACCTATTGCCAGGAAGATAGGCAGCTCATCTGTG
TCCTGTGTCCAGTCATTGGGGCTCACCAGGGCNNCCAACTCTCCACCCTAGACGAAGCCT
TTGAAGAATTAAGAAGCAAAGACTCAGGTGGACTGAAGGCCGCTATGATCGAATTGGTGG
AAAGGTTGAAGTTCAAGAGCTCAGACCCTAAAGTAACTCGGGACCAAATGAAGATGTTTA
TACAGCAGGAATTTAAGAAAGTTCAGAAAGTGATTGCTGATGAGGAGCAGAAGGCCCTTC
ATCTAGTGGACATCCAAGAGGCAATGACCACAGCTCATGTGACTGAGATACTGGCAGACA
TCCAATCCCACATGGATAGGTTGATGACTCAAATGGCCCAAGCCAAG

TABLE 1 194/467

Sequence 1181

Sequence 1182

Sequence 1184

ATTGGAGCTCCCGCGGTGGCGGCCGAGGTACAAGATAGTCATCTCAGTAAAAGGTCTAT
TATCTAACTTGCCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACNGCCATAATGCC
GTGCACAGNTTGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAGTTTN
CTCAAGCAGGCCTGGCTGAAGGCCCAGGAGGGAAGAATATAAGAACCAACAATAAAAA
TAGCAATAGCAATAAGAAGAATGCCATCCCATGGAGCACACCATAATTCTGGAACCACCT
NTCCCGGATCAGGCTTCCATTGCTCACGATGCTCACGCTGGGCAGCCGCAACTNTACTTT
GCAGAACCTCACCAACTTGCCCAGGTNTTCTCCCCGGTCTTGAAGAAATGGCTCTCCACC
TGAAAAGTNNGATCTTCTCCATACCAGCTTCTTAAGCAAAAGCAATCCTCTCTTTGCTTC
CTCAAGGGGCA

Sequence 1185

GGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCAAATGAAGTGTGAAGACAAGG

TABLE 1 195/467

Sequence 1188

Sequence 1187

CCGCGGTGCCGAGGTACAAGATANTCATCTCAGTAAAAGGTCTATTATCTAACTTG CCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACTGCCATAATGCCGTGCACAGCTT GAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTTCNAAGTCCTCAGCAGGCC TGGCTGAAGGCCCAGGAGGGAAGGAAATATAAGAACCAACAATAAAAATAGCAATAGCAA TAAGAAGAATGCCATCCCATGGAGCACACCATAATTCTGGAACCACCTCTCCCGGATCAG GCTTCCATTGCTCACGATGCTCACGCTGGGCAGNCGCAACTCTACTTTGCAGAACCTCAC CAACTTGCCCAGGTATTCTCCCCGGT

Sequence 1189

Sequence 1191

Sequence 1190

TABLE 1 196/467

Sequence 1192

Sequence 1193

Sequence 1194

NGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACACATAAATCACCTGGAACCTTG
TTAAAATGCAGATCCTGACTCAGGAGGTCTGAGTTAGAGCCCAGGATTNCATATTTCTAG
CCAGCTCCATGATGAGCTGCTGGTCCGCAGATCATGCTTGCNGGTTTTGACCAGAGTCAG
TGTTGGTTANAGTAAGAGGATGAGGCANACATNTGGGAAAAGTCCAGCTGGGGCAAGCAT
TTGAAGTCTGCCTTCCTACCANGTCAAAATCAAGGCAACGACCTTCCATAGATAACTATC
AAAGCTTGAGGGGGNGCCTTGAACCCAACTCCTAAATCCCTAAGACCTGCCCACCTCTTG
TGTCTCCTGTNTNAGCAAACATTCCCACACTCTTGCATATTGTTAAAAGTAACCTCTGCT
TACCAGGCTTTTG

Sequence 1195

Sequence 1196

Sequence 1197

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ATACTTTAAATTCACAGCAAATAATCAGACAATTGATGAAAAATACTTACCCAAACACTAA
TTGTAGACTGTGCCTTCTGAATATGTTTTGTCATAAACTTGGAGTAAGGAATCCTCACAG
GCACTGGACAATTCAAAAAACGTAAAGTTTGTTTGTTAGAATACCTGGGTGCTTTTGGAT
AGAAACCCTCATCCATATCCTGGTAAGGCTTGAAGTTGCACAGGAGTTTTCATTTGTCAA
AACCCAGAAAACCATAAGCTTTAGATTTGGG

Sequence 1199

Sequence 1201

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCGGGCACGGTACGCGGGGGTAAC
TGAAAATCCACAAGACAGAATAGCCAGATCTCAGAGGAGCCTGGCTAAGCAAAACCCTGC
AGAACGGCTGCCTAATTTACAGCAACCATGAGGCCACTTAAGGATGCAGCAAGAAGGAGC
CATCTGCAATCCAGGAAGAAATTCCTTGCCAGGAACCAAATTGGTTGTCACCTTCATCTA
GGACTTCTAGCCTCGAGAACTTACAAATGGTGATGATCAT
Sequence 1202

Sequence 1204

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Sequence 1207

Sequence 1208

CCCTTCGAGCGGCCCGGGCAGGTACCAAATGAAGTGTGAAGACAAGGCCATCCAC CACTTTATAGAGGGTGTAAAAATAAACCAGANATCAAGGGAGAAAGAAAAAGATGAAAGAC AAACTGCAAAAAATTGCCAAAATGCGACTTTCTAAAAATGGAGCANATTCTGAGGCTTTG CATGTCTTGGCATTCCTTCAGGAGCTGAATGAAAAAATGCAACAAGCANATGAAGACTCT GAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAAGCTGGAATGAAGAATGA AGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGAGCTGAAATTCCTCCACCA AGTTGGTATTCAAAATATGTAATGACTGGTATGGCAAAAGATTGG

Sequence 1210

Sequence 1211

TABLE 1 199/467

CCCCCGGGGGGGGAAAAAANCCCCCNGGGGGGGAAACCCCCCGG Sequence 1212

Sequence 1214

TABLE 1 200/467

GCATTCCTTCAGGAGCTGAATGAAAAAATGCAACAAGCAGATGAAGACTCTGAGAGGGGT TTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAAGCTGGAATGGGGAATGAAGAATAGAG ATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGCTGAAATTCCTCCCCAAGTTGGTATT CAAAATATGTAATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTGG CAGGGTTATGTTA

Sequence 1218

CCGCGGTGGCGGCCGAGGTACTTCTTACAGTCTTCAGGAAATTCATTAAATCAGTGCCTC
CAGTTCCTTTGGCTCCAGTTTTGAAGGGTCTTCAGAGGTCTTATTCTCCTTTTGGCTGCT
GGCTTGCAGGAATCAGGATGTACTGTTCCTGTTGGCCGAGTGGAGACTGGNGTTCTCAAA
CCCGGNATGGTGGTCACCTTTGCTCCAGTCAACGTTACAACGGAAGTAAAATCTGTCGAA
ATGCACCATGAAGCTTTGAGTGAAGCTCTTCCTGGGGACAATGTGGGCTTCAATGTCAAG
AATGTGTCTGTCAAGGATGTTCGTCGGGGGCAACNTTGCTGGTGACAGCAAAAATGACCCA
CCAATGGAAGCAGCTGGCTTCACTGCTCAGGGTGATTATC

Sequence 1219

CCGCGGTGGCGGCCGAGGTACATTGGCACGTCACGATGTCTTGAGTTTCACTAGGT GGCAGCCTGCATCGTTCCACTGCAAATGACTGAAATCCCAAAACACACAATGAGGCTGGC TCAGGTTTGACTCTATCTTGGAAAAAAATAGGAAAACTTCATTTATGGAATAGTTTTGAA TAACCGTGGATATCACAGGTCCATTGACCTGAGCATTTCCATTTTTGGAAACGGGTAGAA TGTTCCCCAGAGTCAACGAGGCCATGCTGATAATAGTTTCTGGAAGGGATCTCTGGAATT GGTCTGACCCAATTAACACACGGCCTCTGATGGGAATAGATGTATTTTGGGGACACATTT TAATCTGATAGCTGTAACCCCTTTTGAGTTGGCTTTTGTTCACTGGAATCCCTTTCCAGT CA

Sequence 1221

Sequence 1222

CGACTCCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCAAA

TABLE 1 201/467

TGAANGTGTGAAGACAAGGCCATCCACCACTTTATAGAGGGTGTAAAAATAAACCAGAAA TCAAGGGAGAAAGAAAGATGAAAGACAAACTGCAAAAATTGCCAAAATGCGACTTTCT AAAAATGGAGCAGATTCTGAGGCTTTGCATGTCTTGGCNTTCCTTCAGGAGCTGAATGAA AAAATGCAACAAGCAGATGAAGACTCTGAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCT TCAGCATCAAGCTGGGAATGGGGG

Sequence 1224

Sequence 1225

Sequence 1226

Sequence 1227

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTCCAGGAAGTGAAGTAAAA CCTGGTCTTGGTTGATAGGCCCCAGGTTGGCTTGGAGCCATTCCAGGTTGAGAGGCAGGA GCCACAGTATAATTAGTAGGCTGAGAAGTTTGGGCAGTGTAAGTTTGTGCAGGATAATTG CTCGCCTGGTACTCTTGGAAGTCCACCTCGTTGTCCCTGTTGCTGTCCAAGTTGCTCATC AGCTTCTGGAAAGCAGCTTCACCTGTCCTTTTCCCCAAGAAGCTGGGCAGCTCCCGGGTC AGCAGCTCCTTTAGTTCTGACTTGTTGAGCTTGAACTTGTCACCCTCTTTTGCCCGAGTAC CTGCCCG

Sequence 1228

TABLE 1 202/467

TTGAGAGAGCCCAAGGAGTTCTGGGAGAGGGACCAAATGGGGGG Sequence 1229

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCAAATGAAGTGTG AAGACAAGGCCATCCACCACTTTATAGAGGGTGTAAAAATNAACCAGAAATCAAGGGNGA AAGAAAAGATGAAAGACAAACTGCAAAAAATTGCCAAAATGCGACTTTCTAAAAATGGAG AAGCAGATGAAGACTCTGAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAA GCTGGAATGGGGAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAG CTGAAATTCCTCCACCAAGTTGGTATTCAAAATATGTAATGACTGGTATGGCAAAAGATT **GGACT**

Sequence 1230

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGCAGGTACGCGGGGGGTCTTC TAGTCCGGTAAACAGAGGGCCTGCCCCGACAGCTTCTGCTTCCGGGTCACGCCTTGACA GCGGCTTTCAACCCCCACCTCAGCCCAGCAATTCGTTTGGAGCATGTGAACACCTTGAGC CTTGATGAGTTCCAGTNTGTGGTATATTATGCAGNGCNTTCAGNGAAAATNCTTTTTNTN CGGGNNTTNAANNAAAAANANTNGGGTGCCATGNTNTTNCCCCCNNNNNNTNGGGGGGGG GCCCCCTCAAANGGGGGGGGGGACTATNANNNNCCCTNTTTTTTGGGGNNCNANNTNN ACNCCNTTTNNTTNGGGCCCCNTTTTTTGGGGGNAAAAAAACCCCCCCCCTNNGGGGGGG GTATTTCNTTTTNNGAAAAAAAAGGCCCCGGGGNNGACCCCCCCCNGGTGGGNTTAN ANAAAAAAAAAAANTCNCCCNNTTNTTTTTTTTAAAA

Sequence 1231

AGGTACGCGGGGCTTTTCCGTGCTACCTGCAGAGGGGTCCATACGGCGTTGTTCTGGATT CCCGTCGTAACTTAAAGGGAAATTTTCACAATGTCCGGAGCCCTTGATGTCCTGCAAATG AAGGAGGAGGATGTCCTTAAGTTCCTTGCAGCAGGAACCCACTTAGGTGGCACCAATCTT GACTTCCAGATGGAACAGTACTCTTGGAAGTCCACCTCGTTGTCCCTGTTGCTGTCCAAG TTGCTCATCAGCTTCTGGAAAGCAGCTTCATCTGTCCTTTTCCCCAAGAAGCTGGGCAGC TCCCGGGTCAGCAGCTCCTTTAGTTCTGACTTGTTGAGCTTGAACTTGTCACCCTCTTTG CCCGAGTACCTGCCCG

Sequence 1232

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGCAGGTACGCGGGGAAA CAAAAAGGAACCAGAGGCCACTTGTATATATAGGTCTCTTCAGCATTTATTGGTGGCAGA AGAGGAAGATTTCTGAAGAGTGCAGCTGCCTGAACCGAGCCCTGCCGAACAGCTGAGAAT TGCACTGCAACCATGAGTGAGAACAATAAGAATTCCTTGGAGAGCAGCCTACGGCAACTA **AAATGCCATTTCACC**

Sequence 1233

GCNATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCAAANTGAAGTGTGAAGACAAGGCC ATCCACCACTTTATAGAGGGNGTAAAAATAAACCAGAAATCAAGGGAGAAAGAAAGATG AAAGACAAACTGCAAAAAATTGCCAAAATGCGACTTTCTAAAAATGGAGCAGATTCTGAG GCTTTGCATGTCTTGGCATTCCTTCAGGAGCTGAATGAAAAAAATGCAACAAGCAGATGAA GACTCTGAGAGGGTTTGGAGTCTGGAAGCCTNATCCCTTCAGCATCAAGCTGGAATGGG GAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGCTGAAATTNCT CCCCAAGNTTGGTATTCAAAATATGTAATGACTGNTATTGGCAAAAA

Sequence 1234

GCNATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACCAAATGAAGTGTGAAGAC AAGATGAAAGACAAACTGCAAAAAATTGCCAAAAATGCGACTTTCTAAAAATGGAGCAGA AGATGAAGACTCTGAGAGGGGTTTGGAGTCTGGAAGCCTCATCCCTTCAGCATCAAGCTG GAATGGGGAATGAAGAATAGAGATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGCTGA AATTCCTNCCCAAGTTNGGTATTCAAATATGTAATTGCTGGTATGGCAAAAGATTGGACT AAGACACTGGCCCTACCACTGGACAGGGGTTATTNTTTAACCCCCTGAATTTGCTTGGGT

TABLE 1 203/467

CTTTGAGAGAGCCCCAAGGGGGTTTTGGGAGAGGGGACCCANAATTGGGGGGTAGGTC Sequence 1235

Sequence 1237

Sequence 1238

Sequence 1239

Sequence 1240

TABLE 1 204/467

Sequence 1241

Sequence 1242

Sequence 1243

Sequence 1244

Sequence 1245

TGGTACTGCTAAAGTCATGACAGCCCAACAGGTGATGTTTTACTGGATGAAACTCTGAAACACTCAAAGCAACTGAAACCCACAGAAACTGTCCAAACATGGATAGAGCTACTCACTGGTGAGACCTGGAACCCCTTCAAATTACAGTACTGTTCCTGTTGGCCGAGTGGAGACTGGTGTTCTCAAACCCGGTATGGNGGTCACCTTTGCTCCAGTCAACGTTACAACGGAAGTAAAATCTGTCGAAATGCACCATGAAGCTTTGAGTGAAGCTCTTCCTGGGGACAATGTGGGCTTCAATGACAAGAATGTGTGTCAAGGATGTTCCGTCGTGGCAACCGTTNCTGGTGACAGCAAAAAATGACCCCACCAA

Sequence 1246

Sequence 1247

TABLE 1 205/467

GGACTAAGACACTGGCCATACCACTGGACAGGGTTTATTGTTAACACCTGAATTGCTGGGGTC

Sequence 1248

Sequence 1249

Sequence 1250

Sequence 1252

TACTTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACAATCTTGAGAAGGATTT GAAGGACAAGTTTGTGGCCCTGACCATAGATGATATCTGCTTCTCGCTCAACGACAACTC ACCAAACATCAGATATTCTGAGAACGCCGTGAGGATTGAGCCAAACTCCGTGAGTCTGGA AGACTGGTTGGACTTCTCCAGCACCAATGTGGAGAAGGCTGACAAGCAGCGGAACAACTC CCTGATGCTGAAAGCCCTGGTGGATCGAATCCTGTCCCAGACAGCCAATGGATCTGTGCA AGCCAGTGTGATTGTGGTGGACACCGGCATTCAAGAATGGGCCTGAAGGGATCAAAGGGA TGCCAGGGACAAGCTGGGCTTGATCATCTGGCCCAAGGTATTNGGAAAGAGATTGCTTCC CAGGGAAGAAA

Sequence 1253

TABLE 1 206/467

CTGAAATTCCTCCCCAAGGTTGGTATTCAAAAATATTGTAATGAACTGGGTATTGGCAA

Sequence 1254

CCGCGGTGGCGGCCGNGGTACAATGATTGTCATCTCAGTAAAAGGTCTATTATCTAACTT GCCAAACTTGTTTACTGAGAGCCCTAAGGAACTAAAACTGCCATAATGCCGTGCACAGCT TGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCCTTCCAGTTCCTCAGCAGGCC TGGCTGAAGGCCCAGGAGGGAAGGAAATATAAGAACCAACAATAAAAATAGCAATAGCAA TAAGAAGAATGCCATCCCATGGAGCACACCATAATTCTGGAACCACCTCTCCCGGATCAG GCTTCCATTGCTCACGATGCTCACGCTGGGCAGCCGCAACTCTACTTTGCAGAACCTCAC CAACTTGCCCAGGTATTCTCCCCGGTCTTGA

Sequence 1255

Sequence 1256

Sequence 1258

Sequence 1259

TACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCCGGGCAGGTACTCTTTGTTT
TGGCACACTTTTCCTGACAAACAGCCAGTGTTCTCAATACATAAATACTAGTCCACGTTA
ACAACAATAGCATATGAGACCGCTCTCCGTAAAGATGCCAGATTGGATGCAAATGGACTG
GAAATACCTTGGAGGGTTTCACAAAAATAAGACAAAGGGCAAAGGAACTTTGCCAAAGGA
GATGGAGGAGCAATTCTTTAAAGATAGTGGGAGGAAGCAAAGAGCTCATAAATACAA
GCCTCTTAAAATGGGACGCATTTGCCTCGCGCCTCTGGGGTGTCTGCAGCTCAGCNTTGG
TGCCCCACACGGGACACCCGACTTTT

Sequence 1260

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Sequence 1261

Sequence 1262

TGGCGCCGCCGGCAGGTACGCGGNGCAGAAGAGAGAAGATTTCTGAAGAGTGCAGCTGCC
TGAACCGAGCCCTGCCGAACAGCTGAGAATTGCACCATGAGNGAGAACAATAAG
AATTCCTTGGAGAGCAGCTACGGCAACTAAAATGCTTTCACCTGGAACTTGATGGGAGGG
AGAAAACTCCTTGGATGATTTTGAAGACAAAGTATTTTACCGGACTGAGTTTCAGAATCG
TGAATTCAAAGCCACAATGTGCAACCTACTGCCTATCTAAAGCACCTCAAAGGGCAAAAC
GAGGCAGCCCTGGAATGCTTACGTAAAGCTGAAGAGTTAATCCAGCANGAGCATGCTGAC
AAGGCAGAAATCAAAAGTCTGGTCACCTGGGGAAA

Sequence 1263

Sequence 1264

GGCGAATTGGACTCCACCGCGGTGGCGGCCCGAGGTACAGAGATTTATAATGTGCTGCTC
TAGGTCCTATCGGGTAAAGGGATCAGCAGATGTGAAGTCAAGAGTCTCCTGTAAGATTTG
ACTITCTTGGAAACATATTTTAATCCTGGGCCTCCTNTTTCAAATCACCTATTTCTTTTA
GTTTTTTGCAGTGATACTGTGTTGCTTCTAACAGAGGTTCAGTTTCACAGCCTTTCCC
TCAAGTGTCTTATCCTAAAAGTAAAACCTAGATGATCTAAGGTGGTGGNTTTCAACAGGG
TGCAAATTTGCCTCCTATACTCGCAACACCCAGNGACAGTTGGCTAATGTCTNGGAGACAT
TTTTGNGTTNTCACACCTGGANNNAGGGTGGGGGAGGTGGNGCTAATGACANCAAGNTGG
CCNTAANCCAATNATGCTGATANAAATNCTACANTGCACAAGGATAGGNTCCCACANAAC
ANAAGNCTTANCCAAACCCCAAATACTAACAAT

Sequence 1265

CCGCGGTGGCCCGAGGTACAAGATAGTCATCTCAGTAAAAGGTCTATTATCTAACTT GCCAAACTTGTTTACTGAGGAGCCCTAAGGAACTAAAACTGCCATAATGCCGTGCACAGCT

TABLE 1 208/467

TGAAAAGCAATTAGAGTAAGCAAGATTAGTTTTTCCTCCTTCCAGTTCCTCAGCAGGCCT GGCTGAAGGCCCAGGAGGGAAGGAAATATAAGAACCAACAATAAAAATAGCAATAAGCAAT AAGAAGAATGCCATCCCATGGAGCACCCATAATTCTGGAACCACCTCTCCCGGATCAGG CTTCCATTGCTCACGATGCTCACGCTGGGCAGCCGCAACTCTACTTTGCAGAAACCTCACC AACTTGCCCAGGTATTCTCCCCGGTCTTGAAGAAATGGCTCTCCACCTGAAAAGTTGATC TTCTCCATACCAGCTTCCTTAAGCAAAAGCAATCCTCTCTTTGCTTCCTCAAGGGGCAGC ACAAAGGATGTTTTGGCTGTGGGAAACAGAAGCCCGCATTTGTAGTTGCACTGGCGAGT GAAGTGATAGTTGACGCTGGTTGGGGTGGT

Sequence 1266

CCGCGGTGGCGCCCGGGCAAGGTACTTGCTAACTTTGACGCCAGCATCTCTGAAAGATCCCCATCGAAGGCCGGTCATTGCAAATACAGGCTGTTCCTTTTCACCCTTGATCTGCAAGACATCAAGTGGAACTGTCTCTCCTTTCACAATGGCAAGTGTGGCATCAGTAATATGTTGGACTTTGTTTCCACTTTCGGCAAAGAGGGTATGACTCAAACTACTGGTCTCTCCCAGTGGGATAAATCCAATGGGAATCTTACTGAAGGTAGCCTCATCTGTTCGTCGAAGAACACCAAGTAACAACCTNCTGCAGTGTCCCATCTCCTTCCTGNAACAATGGATCACATTCCGGNGTTTTCCATCAGTTNCAAGGAGGTTTNTTNGGCTTGGGCCCTTAANAAATCTGNGCTTAAACAAAAAGGCCCNATTCCTTCCCAAATAAAAANGGAAAAANTCGGGGGCCNCAATTTTTTTT

Sequence 1268

Sequence 1269

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTTCTACAG
AGATCCTGAAGAGATTGAAAAAGAAGAGGCAGGCTGCTGCTGAGAAGGCAGTGACCAAGGA
GGAATTTCAGGGTGAATGGACTGCTCCCGCTCCTGAGTTCACTGCTACTCAGCCTGAGGT
TGCAGACTGGTCTGAAGGTGTACTCTTTGGTTTATCAATGGGACGTTCCAGCAATCCACAC
AAGAGCTCTTTATCCCCAACATCACTGTGAATAATAGCGGATCCTATATGTGCCAAGCCC
ATAACTCAGCCACTGGCCTCAATAGGACCACAGTCACGATGATCACAGTCTCTGGAAGTG
CTCCTGTCCTCTCAAGCTGTGGCCACCGTCGGCATCACGATTG

Sequence 1270



Sequence 1271

Sequence 1272

Sequence 1274

Sequence 1275

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Sequence 1277

AGGTACAAAATTATCATCATTTAGAGTTGATTTTTTTCACCAGCCCTGAATTTCAAACT
TGTAATATGCTGTTTCACAATCTTTTTATTAAAATTACTTAATGATTCCAGTNTGGCAAAT
GAGCCATAGACTTTTGCTCTGCTTGTTATAAGATCANTTGGAATTGGGNGGGGGGGANAA
CCANTAGTTAAGNCTAAATCTAATCCGGTCACTTGGCTTCATTGTAAAAGAACCCCACAA
TTGGTCTGAATTAATTTTTTGCCCAGGCACCANGAAAGNAANATNGNTGTACCAAAGNTN
GAANTACATTCCTTGGCAAANTGGGGCCCTCTTTGGCCCAAATCCTTTTTTCCAATTATC
CTTATTGGTTAAAACCCTTTTTTTGGTTAAGTNTNACCTTGGGTGGTTGGAATNTTTAAA
GCCGGNCTTGGNNGGCCTTAATTTTGGTAAAAAATTTCTTTTGGGGGATTTTAAAATTTA
AACCCAANAANAACCANACCAAANAAATANTTCNTNATTNCACCCCTTGGGGNAAATTNA
TTTTGGGAAAAAGGAAAAAAATTTCNAAGTTTAAAAAACCCAAAGGAANTGGGTNGTTCC
TCCAATTANGGTNTTAAAAGGG

Sequence 1278

Sequence 1279

GTGGCGGCCGAGGTACCAANTGAAGTGTGAATGACAATGGCCATCCANTANTTTATAGAG GGTGTAAAAATAAACCAGAAATCAAGGGAGAAAGAAAAGATGAAAGACAAAACTGCAAAAA ATTGCCAAAATGCGACTTTCTAAAAATGGAGCAGATTCTGAGGCTTTTGCATGTCTTGGC ATTCCTTCAGGAGCTGA

Sequence 1281

CCGCGGTGGCGCCGCTCGGGCAGGTACCATTCCTCTACATCCATTTGGTAGCAGAACCT CAAGTGTAAGCAGTCAGTGTAGCATGAATATGAACTGGCTCAGTTTATCACTTCCTGTTT NGACCTGAAGCACCACCCAGCTATGCAGAAGTGGTAACAGAGGAACAAAGGCGGAACAAT CTTGCACCAGTGAGTGCTTGTGATGACTTTGAGAGAGCCCTTCAAGGACCACTGTTTGCA TATATCCAGGAGTTTCGATTCTTGCCTCCACCTCTTTATTCAGAGATTGATCCAAATCCT GATCAGTCAGCAGATGATAGACCATCCTGCCCCTTTTGTTGAAGGAACACTTGGTTGA Sequence 1282



TABLE 1 211/467

Sequence 1283

GGTGGCGCCCGNCAGGTACCAAATGAAGTGTGAAGACCNGGCCATCCACCACTTTAT
AGAGGGTGTAAAAATAAACCAGAAATCATGGGAGAAAAGAAAAGATNAAAGACAAACTGCA
AAAAATTGCCAAAATGCGACTTTCTAAAAATGAGCAGATTCTGAGGCTTTGCATGTCTTG
GCATTCCTTCAGGAGCTGAATGAAAAAATGCAACANGCAGATGAAGACTCTGAGAGGGGT
TTGGAGTCTGGAAGCCTCATCCCTTCANCATCAANCTGGAATGGGGAATGAAGAATAGAG
ATGTGGTGCCCACTAGGCTACTGCTGAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTAT
TCAAAATATGNAATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTG
GACAGGNTTATGTTAACACCTGAATTGCTGGGTCTTGAGAGAGCCCNAGGAGTTCTGGGA
NAGGNACCACATTGGGG

Sequence 1284

CGCGGTGGCGGCCGGGCAGGTACCCCGGGAGAGCCCGCTTCCCCCTCCTCCTGTG
CTGTCTCCACCCGAGGAGAGCGGCCTGCCCGGAAGTGGGCCACCATATCTGGAAACTACA
GTCTATGCTTTGAAGCGCAAAAGGGAATAAACATTAAAGACTCCCCCGGGGACCTGGAGG
ATGGACTTTCCATGGTGGCCGGAGCAGCAGCTTACAATGAAAAATCAGAGACTGGTGCT
CTTGGAGAAAACTATAGTTGGCAAATTCCCATTAACCACAATGACTTCAAAATTTTAAAA
AATAATGAGCGTCAGCTGTGTGAAGTCCTCCAGAATAAGTTTGGCTGTATCTCTACCCTG
GTCTCTCCAGTTCAGGAAGGCAACAAGCAAATCTCTGCAAGTGTTCAAAAAAATGCTGAC
TCCTAGGATAGAGTTATCAAGTCTGGAAAGATGACCTCACCACACATGCTGTTGATGCTG
TGGTGAATGCACCAATGAAGATCTTCTTGCATGGGGGAGGCCTGGCCCTGG
Sequence 1285

CGCCGGCAGGTACCAAATGAAGTGTGAAGACANGGCCATCCACCACTTTATAGAGGGTG
TAAAAATAAACCAGAAATCAAGGGAGAAAGAAAGAIGAAAGAIGAAAACTGCAAAAAATTG
CCAAAATGCGACTTTCTAAAAATGNGCAGATTCTGAGGCTTTGCATGTCTTGGCATTCCT
TCAGGAGCTGAATGAAAAAATGCAACAAGCAGATGAAGACTCTGAGAGGGGTTTGGAGTC
TGGAAGCCTCATCCCTTCAGCATCAAGCTGGAATGGGGAATGAAGAATAGAGATGTGGTG
CCCACTAGGCTACTGCTGAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTATTCAAAATA
TGTAATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTGGACAGG
Sequence 1286

TCGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCGCCCGGGCAGGTACAGGTAAGATATA CTGGAGTCACAGAGCAATATGCATTAACAGGATACAACAGTTCATAAAAACTGAGTAACT ATGCACACAAATTTCTTAAACAGCCACCTAAAGAGAAAATGCACAGATGTATGGTGGAAA CTGTATCTAACACTGAAACTACTACAGGACTCCATCAATGAGTCCAACTTTTAGTGATAA AAAACTACTGTACACTACATGAAGAACCATATGTTTATAATTATCCAAAATAAAAATGAAG TTATTAAACTTCAAGATAATATGGTAATTTGCATTGAACCGATGATTTTACAAAATTCTG CAAAGGTCAAAATTTTAAAAGATGGCTGAACAGTAATTGCAGCATCTAATAAAAAACCGCAG CTCATTACCGAGCAAACGGTTTTAATTAAAAATTCAAAAGGAATAATCCTGACAGGAGAA ATAAAAAAAATAGATGTCAAAAGAAGAAGATAATTTTTCAAAGGAGTAGTAACTCAAGTT TTAACACC

Sequence 1287

Sequence 1288

CCGGGCAGGTACAAGATAGTCATCTCAGTAAAAGGTCTATTATCTAACTTGCCAAACTTG

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Sequence 1289

Sequence 1292

TABLE 1 213/467

CCGGGCAGGTACCAAATGAAGTGTGAAGACAAGGCCATCCACCACTTTATAGAGGGTGTA
AAAATAAACCAGAAATCAAGGGAGAAAGAAAAAGATGAAAGACAAACTGCAAAAAATTGCC
AAAATGCGACTTTCTAAAAATGACAGATTCTGAGGCTTTGCATGTCTTGGCATTCCTTCA
GGAGCTGAATGAAAAAAATGCAACAAGCAGATGAAGACTCTGAGAGGGGTTTGGAGTCTGG
AAGCCTCATCCCTTCAGCATCAAGCTGGAATGGGGAATGAAGAATAGAGATGTGGTGCCC
ACTAGGCTACTGCTGAAAGGGAGCTGAAATTCCTCCACCAAGTTGGTATTCAAAATATGT
AATGACTGGTATGGCAAAAGATTGGACTAAGACACTGGCCATACCACTGGACAGGGTTAT
GTTAACACCTGAATTGCTGGGTCTTGAGAGAGCCCAAGGAGTTCTGGGAGAGGGACCAGA
TTGGGGGGTAG

Sequence 1294

Sequence 1295

Sequence 1296

Sequence 1297

TABLE 1 214/467

TTCTGGGGAGAGGGACCAGATT

Sequence 1299

Sequence 1300

Sequence 1302

Sequence 1303

Sequence 1304

Sequence 1305

AGGTATTCGACCCACGCGCCCGTAGTTTTTATCTTTGACCAACCGAACATGACCAAAAAC

TABLE 1 215/467

Sequence 1307

ACTTTTTTTTTTTTAAGCTGCTCCTTGAGGATAAGGGCTAACTCACAGGCAGTGCA CCAAGAGCCACTATAAAAAGATCCTTAATGAGCAAAATATATCCCCTATTATTTTCCTAC AAGTTGCTTTTTACTTGAGTAGGAACCCTTGATTGATTTTTGCGGACGCGTGGGTCGAAG CTTGACCT

Sequence 1308

Sequence 1309

Sequence 1310

GGGGGGCATTTCACGCTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCCGGGCAGGTCGCCCCGGGCCCCGGGCCCCGGGCCCCGGGCCCATGTTACCAATCTAAATGAA

TABLE 1 216/467

CTGTCTATGCATAGAAAACTGCTTTATGCCTAAGATAATTACTGGGATTTAAGAAAGTGA GAAAAAAGAATAGGTGGGATTGAGAAATTAGGTAAAAACAGAAGAGGCCAACTAAACCCA AGTGCTGCCCTTCAAGGGCTCTAGTAACCGGACGCGTGGGTCGAAGCTTGACCT

Sequence 1312

Sequence 1313

Sequence 1314

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTAGATGACAACATC
AAAACATACTCTGATCACCCCGAGAAAGTAAACAAAGATGATGAGGAATTCATAGAAAGC
AATAAAATGCATGCTATTAATGGAAGAATGTTTGGAAACCTACAAGGCCTCACAATGCAC
GTGGGAGATGAAGTCAACTGGTATCTGATGGGAATGGGCAATGAAATAGACTTACACACT
GTACCTGCCCGGGCGGCCGCCCGGGCAGGTCCGGGCAGGTGCTGTGAGTGCTCTGG
CGAAGTTTGGAGCCCAGAATGAAGAGATGTTACCCAGTATCTTGGTGTTGCTGAAGAGGT
GTGTGATGGATGACAATGAAGTAAGGGACCGAGCCACCTTCTACCTAAATGTCCTGG
AGCAGAAGCAGAAGGCCCTTAATGCAGGCTATATCCTAAATGGTCTGACTGTCCATCC
CTGGTCTGGAGAGGGCTCTGCAGCAAGTACCT

Sequence 1315

Sequence 1316

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCTTCGACCCACGCGTCCGCGAAAAGATGAGGCAACAAGTAAGAGAAAACAGCATTGAGCTTAGAGAATTGGAGAAGAAAT

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TABLE 1 217/467

TAAAAGCAGCTTACATGAATAAAGAAAGGGCAGCTCAGATTGCTGAAAAGGATGCCATTA AATATGAACAAATGAAACGTGATGCTGAAATAGCCAAAACCATGATGGAAGAACACAAGA GAATAATAAAGGAAGAAATGCTGCAGAAGACAAACGAAACAAAGCGAAAGCACAGTACC TGCCCG

Sequence 1317

Sequence 1319

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Sequence 1323

Sequence 1324

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCACGCGTCCGCAGAGGCCC
AGGCTCCCAAACCGACAAAGTGAAAAGAGACCAGAGAGGCCAAGCATATTGACTGGTGCT
GTTCAGGGCCTGCTCTTTTCCACCACCTTGTTTTGCTGCTTGTCACGAGGAGAGTTG
TTCCTGTATGTGGCTGCTCTCAGATCTTTCCAAGCAAGCCAGTCATTTGAAGAGGTTTTC
TTTTCATGCTGGAGGGCAGGCTAAGATCAATGAGTGGAAGAGAGAAAGGCTGTTTTAGCT
CAAGTTAAAGGAACACCTTCTAGCCATCAAAGCCGCCCAACAGAGGCAAGGGCCACCACA
CATGAGAGAGAGCGCTCTNTCCTTAA

Sequence 1326

GCGAATTGGAGCTCNCCGCGGTGGCGGNCGCCCGGGCAGGTACCAAAATAATTACCAACA
NTACATTATGTACACCATTTACAGGAGGGTAACACAAACCTTGACAGGTAGTAACTTTTC
ACCCCACATNACTGAACGCTTAACACTCCTGGCTGTTAATTGTCAGTTCAGTGTTTTAAT
CTGACGCAGGCTTATGCGGAGGAGAATGTTTTCATGTTACTTATACTAACATTAGTTCTT
CTATAGGGTGATAGCGGACGCGTGGGTCGAAGCTTGACCT
Sequence 1327

TTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCTGTAGCCTATGACTTG
AGTCTCTTGAACTTCTAGGAAGAGGCAAACTACAAACTACTAGGATTCTGATTTCAGATA
TAGGCATTCCAGAATCTTCTCTTTACGAGTTCACCTGCTAGTATAATCTCCACAACTTGA
ATGGCCTTGGTTGTTCTGTAATTGCTGCCAAAATCATCACAAGCTGTACCTGCCCGGGCG
GCCGGCCGCCCGGGCAGGTCAAGCTTCGACCCACGCGTCCGGATGGGAATTCAGGTATGA
AAGAAAACAGGCAAGGAGCACTGAGGGAGAAAGACACAGACTTTATCGCTCTGTGGCTC
ATTGTTACTGGAATATTCTAAAACTCTTGTTCACATGCTATTATGACTTATAAAGCAGCA
ACAGCTGAGGCGCACCAGGACACAGCTTCCATTTCTTTAACGT

Sequence 1328

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Sequence 1329

AGGTCAAGCTTCGACCCACGCGTCCGTGAACTTTTATCAAGGCTTTTGCTCTTTTAGACT
TGAGTTTATCTTTATAATTAAGGAGAATGGTTTTTAAAATTTAGTTCCTCTGACACCCCA
AAATTATCAAAATAAATTATGTTGTAGTGAATCTGTTTTTGAAAGTCATTGATAGGACT
TATATGAGTCAAAATTTTATGGATTATAAACTAGGCTTTATCTGGTTGGAAATAATTGCA
ATACAAGAAGCAACTTTATTAAATTAGACCTAAAGTCACAATCTTCTTCTTTGCTGCTTT
TTAAAAATTACCTATTACCTTTAAAAGATCCCAAATTTAGAAGAGGAATTAAAATAAAAG
TTAATGCAATAAAACACTTCCACAATATTCTATTACTTCAACCTCTAATCAATGAAA
Sequence 1331

ACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTTTCCTGCATTTC
TAATGAAGAAATAGGCTGGTCCTCAATTTTGCAGAAGTTGTATCATCATAGGTCATACCT
AACATTCGTTTGTCAAGAGCAAAAAAACCCCCTTGGGTTCTCTGGATCTCACACAGCCCA
CAAACCTTCAGAATGTGGTTCCTTCCCGCAGGCTTTGTCACACTTAAGATCCAAGAACAA
ATCAGCCTGGCTTTAACATGGGGTAGATGGCAAGAAGGATAATGCGGACGCGTGGGTCGA
AACTTGACCT

Sequence 1333

Sequence 1334

TABLE 1 220/467

TATATAAACTTCTGCTTTGGTCTAAAACTGATATATCTTCACGTTGAGGTTTCATCTGAA ATGCNCCACCGTTTGCTGACTTGCTTCAATATGAATTTGGATGGCTATAAAATTGACCTC GGCCGCTCTAGAACTAGTGGGATCCCC

Sequence 1335

Sequence 1336

Sequence 1337

CCGCGGTGGCGGCCGGCCGGGCAGGTGTCCCCATGAGGGCCAGGCCAGGCAGAACCCAT CCCATTTTATCCTTAAACTCAGAAGGAAATNNGTCTAAATATTAAAGGATTAATATGGGA ATAAAAAATGAACCTTAAACCCTGCCACTGATACACAAGCTGTCTCTCTTAGAGTTCAAT GAACACTTCAGGAGAGTATTTCCAACAATATTTAGATATTGGAATATCTAAATATTGTTG ATTTAGATAACCACCCTAGATTTCTCACCACCCTAGAACATTTAGNGGGGAGACATTCTT TTCTCCTTTTTCTGATAACTTGGTCAGAAGTGATTGACTGTGCAAATGGTATTTCTCAGC TAAAATCTCCCTTATGAACCCTTCCTCGAAATCCCAAGGT Sequence 1338

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGATTCTCTGATTAGATTTTAAACTT
TTTTGATGAAATATTGAGTCTTAACTACTTTAAGATGCCATAATACTGAATACAGNGCTA
AGCAAAATAAATATTGACTAGTTCTCATTTCTATCTTTCAAATATTTCTAATGCTCCTCT
TTTATAGCATGGGCTCAGGTATCAGATGGCGTAGGTCAAGATCTTGGCTCTACTGTTTAC
TTACGGGAAATACTTTTATGTTGCTAAATCTCAGTTTTCTCTTCTGTAAGACGGGATTAA
AGTACCT

Sequence 1340

TABLE 1 221/467

AAAAGCCAAGAGTGAAGCAGGGTTGTTTTTCATCCAATTCTTGGTCTTTTTTGTTAAAGGCAGCAATAAGATAGGTGGTTTCGGGCAATCACTTAGCTAATTGGCTCTCTATAGTCATACCTGGATAATATTTGTAGTCATACCTGGGATAATATTTAAAGGGAAGAAACTAAACATAGTCCTTAAGTAGGAACCAACTACAAT

Sequence 1341

CCGCGGTGGCGACGTCCTAGCTTGAGTCGACCCACGCGTCCGGCCGCTGTTCGTAT
TTCTTATTCTACAACAAGGGNGCAGCCTANAGGCAAAACACATCCCATTGTCATTTTTT
GTAAATAAAGTTGTATTGGAACATGGCCACTCTCATTTGTTTTCTATTATTATGGCTGC
TTTCACTTACAACCTGAGTGGTTGCCACAGAAACTGTATGGCCTGCAAAGTCTAAAATAT
TTACTATGTAGCTTTTTCTTTTTTGGAGACAGTGTGCCACTCTATTGCCCAGGCTG
GAGTGCGGTGGTGTAATCATGGCTCATTGCAGCCTCAAACTCCTGGGCTCAAGCAATCCT
CCCGCCTCGGTCTCCCAAGTAGTTGGGACTACAGGCATGAGCCACCATACCCGGCTAATT
TTTTTAAAGTTTTTGGTAGAAATGGAGTTTTTTAATGTTGCCCAGGCTGGTCTTGAACTC
CCTGGTCTTAAATGACCCTTTTCCCATCAG

Sequence 1342

Sequence 1344

CCGCGGTGGCGCCCCGGGCAGGTACCAAGTTTGAGTTGAAACGGTATGTGACTTCCC CAGCTGCACCCTGGGCAGTGACTGCATCACTGAGAGGTCCTGTCTACAGCAGATAA AACTCCACAGATCACTCCTCTGTAATCCCTCTAAGTGCTCCAAGGCAGCAGAAAGGCCC AGTGCATTGAGGCTGGAAGCAGGAGCAGAGACTCTGGGATATAGTGCGAAAGTCTCTTTC CCCTGTAGTTGGGCTAATCTGGAAAAACTCAAAAACCTGGCCTGATTACCGAGGTTTCTT TTATGGATATTTAGATAAAAATTTTTACAGTATTCTTGAAATGAACCCAATTAA ACACATAGTTCTCAGTCTTGACCACACACACTTAAGAATCATCTGGTAGACTTCTGTAAACTA CCAATGCCTGGCCA

TABLE 1 222/467

Sequence 1346

Sequence 1348

Sequence 1349

Sequence 1350

Sequence 1351

Sequence 1352

TABLE 1 223/467

Sequence 1353

TATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGATTCTCTGATTAGATTTTAAACTT
TTTTGATGAAATATTGAGTCTTAACTACTTTAAGATGCCATAATACTGAATACAGTGCTA
AGCAAAATAAATATTGACTAGTTCTCATTTCTATCTTTCAAATATTTCTAATGCTCCTCT
TTAAGCATGGGCTCAGGTATCAGATGGCGTAGGTCAAGATCTTGGCTCTACTGTTTACTT
ACGGGAAATACTTTTATGTTGCTAAATCTCAGTTTTCTCTTCTGTAAGACGGGATTAAAG
TACCT

Sequence 1355

Sequence 1356

TABLE 1 224/467

Sequence 1358

Sequence 1359

CCGCGGTGGCGACGTCAAGTTTCGACCCACGCGTCCGCATTATCCTTCTTGCCATC
TACCCCATGTTAAAGCCAGGCTGATTTGTTCTTGGATCTTAAGTGTGACAAAGCCTGCGG
GAAGGAACCACATTCTGAAGGTTTGTGGGCTGTGAGAATCCAGAGAACCCAAGGGGGTT
TTTTTGCTCTTGACAAACGAATGTTAGGTATGACCTATGATGATACAACTTCTGCAAAAT
TGAGGACCAGCCTATTTCTTCATTAGAAATGCAGGAAACCTGCCCG

Sequence 1361

CCGGGCAGGTCTACTCAAGTAGTCTTTACCCCCTACTCAAGTAGGGGGTAAAGTGTAGAA CAAGGAGTTTGATCTGTGTTCAACTGATTGTGAACCATCAATTGAGATAACTCACTACCT TCAGGCCAGCCAGTTACATACTTTTGAAAAGCCAAGAGTGAAGCAGGGTTGTTTTTCATC CAATTCTTGGTCTTTTTGTTAAAGGCAGCAATAAGATAGGTGGTTTCGGGCAATCACTT AGCTAATTGGCTCTCTATAGTCATACCTGGATAATATTTGTAGTCATACCTGGATAATATTTAAAGGAAGAAACTAAACATAGTCCTTAAGTAGGAACAACTACAATTTTAAC Sequence 1362

Sequence 1363

Sequence 1364

CCGGGCAGGTCAGGAGTGTCCCAAAGATTTCCCAAGTCCAGCCCAGAGAAGCTGAAAGCC TTTCCCCCAGGTGTGGGGCTGAGTTAGATGTGGGTCATAAAGGATGTGGCCTCGAGGCTG GGAGGCAGCTGGGCAAAGTGGGAAGCCTCCCTACTCCTGAGACAGTGATGGCTCAAATCC AGGCCAACCTGGAACATGATCCTCAACTTCTCTAAGTTCACCTTTCCCAGGTGTGAAATG WO 01/070979

TABLE 1 225/467

Sequence 1365

CTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTCTTGAGTCG ACCCACGCGTCCGGAGCTGCTCAATAGTGAGAATCAGGTGATATAATGCATGTGGAAAAA GAATGTGAAAAATCTAACACTTTAGATTGTATACAGTGTTTTTTTAAAAAGACACAAAAAA ACTGTCAACATGAGAAACATAAGCAAAGTTTTACTCAAGACAAACATCCACGAGTCACAA CTTCAGTTATTCCCAGTCTTCAAAATAACAGAAGGGCAAAGCAAAGGTAAACATGCAAA Sequence 1367

GACTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGATTCTCTGATTAGATTTT
AAACTTTTTTGATGAAATATTGAGTCTTAACTACTTTAAGATGCCATAATACTGAATACA
GTGCTAAGCAAAATAAATATTGACTAGTTCTCATTTCTATCTTTCAAATATTTCTAATGC
TCCTCTTTTATAGCATGGGCTCAGGCATCAGATGGCGTAGGTCAAGATCTTGGCTCTACT
GTTTACTTACGGGAAATACTTTTATGTTGCTAAATCTCAGTTTTCTCTTCTGTAAGACGG
GATTAAAGTACCT

Sequence 1368

CCGCGGTGGCGCCGTTAAAGGAATAATCTGCAGAACATCTTGATTTACAAGGGACAAAA TGATGCAAATTATATGCTGTCCAACCTACTGGTGAACTGGATCAGAATGGTCCAAGGACT GTTAAACAGAGGAAGTTTACATTCTGAAAACTTGCGGACGCGTGGGTCGAAGCTTGTA CACCTCGGCCGAGGTACCTTCTGTCACAAAGACCCAAGCTTCCTCCAGCTTCCAGGATAG CAGTCAGCCAGCTGGAAAAGCCGAAGGGATCAGGGAGCCAAAGGTGACTGAAA GCAACAATCACCTAAATTACAGTCCTCCAAGAAAGTTGCTTTCCTCAGGCAGAATGCCCC TCCCAAGGGCACACACACACACACCGGCTGTGTTATNCCCATCCAAGACTCAGGCCAC CCTGAAACCTAAGGACCATCATCAGCCCCTTTGGAAAGGCC

Sequence 1369

CCGGGCAGGTCGAGCGGCCGCCCGGGCAGGTTTCCTGCATTTCTAATGAAGAAATAGGCT GGTCCTCAATTTTGCAGAAGTTGTATCATCATAGGTCATACCTAACATTCGTTTGTCAAG AGCAAAAAAACCCCCTTGGGTTCTCTGGATCTCACACAGCCCACAAACCTTCAGAATGTG GTTCCTTCCCGCAGGCTTTGTCACACTTAAGATCCAAGAACAATCAGCCTGGCTTTAAC ATGGGGTAGATGGCAAGAAGGATAATGCGGACGCGTGGGTCGAAACTTGACCTN Sequence 1370

CCGCGGTGGCGGCCGGCCGGCAGGTGTCGACCCACGCGTCCGACGACTCACTATAGGGA TCTAGATCACGAGCGGCCGGCCGGGCAGGTACAGAGATTTAAATGAAATCTTCGAA AGAATAAATTTGCTTTTCAGTCCACTGTATTTTCAAAATTT Sequence 1371

TABLE 1 226/467

Sequence 1372

Sequence 1373

CCGCGGTGGCGCCCCGGGCAGGTTATAGACAATATGCTCCTTAAGGTCCCTTTCAGT CCCGTTCTATGGATCTGTGTAGTTTCGCTTCTTTTTTCAATATGCTCAGAATTAGGACAC CAATGTTAATGGAAGATAAGGAAACTATACCACCTATCCCTTATAGAAGATTTGTGCACT AACTAATATGAGCCCTGGAAGATCAAGCCAGTAGAAGATCAACTATCCCTGCTTTA TACTTTGGATCATTTATTTGTGAAGATCACAACTTTCAAAGTTTTATTATTTCTTAGGTC TTCATGGAAGTTCGGGGAAATTAACTGGATCTACTTCTAGTCTAAATAAGCTCAGTGTTC AGAGTTCAGGGAATCGCAGATCTCAGTCATCTTCCCTGTTGGATATGG Sequence 1374

Sequence 1375

TACGACTNCTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTCCGGCCACATTTTCAATTTAGCCATTTTTCTCTTATTCACCTTTTTCTCTAAATTCCACTAAATACTCCACTAAGAAAAGTCAATAGATAATTCCAATAATGACTTCACTCCTGAGAAATTTATTAGCTGCTAACGCTTGTCTCATCATAAGCACTCATATGTTCATTGAGTAAAATTTTATTGAGTATTTGCTATGGTCCAGGCACTGTGCTAAGTATTGAGGATAAAATGGTGATTGAAACATTTTCCCTTCTTGATTTTAACATCTACAAAATAAAA

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Sequence 1378

Sequence 1381

Sequence 1382

Sequence 1383

Sequence 1384

TABLE 1 228/467

Sequence 1385

Sequence 1386

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTCAAGCTTCGACCCACGCGTCCGAGAAGAGTTTGCAAATGCAACAAAATATTTAATTTACCGGTTGTTAAAACTGGTTTAGCACAATTTATATTTTCCCTCTCTTGCCTTTCTTAATTTGCAATAAAAGGTATTGAGCCATTTTTTAAATGACATTTTGA

Sequence 1387

Sequence 1388

TTAGGGCGATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACAAATAAGCCCACC CCACTAGGAACTATGTTAAAAAAAAATTCAAGAAAGAATTTAAGGGAGATTACAGTGTTA CTGTGACACCAGGAAAACTTAGAACTTTGTGTGAAATAGACTGGCCAGCATTAGAGGTGG GTTGGCCATNANAAGGAAGCCTGGACAGGTCCCTTGTTTCAAAGGTATGACACAAGGTAA CCCNTAAGCCAAGGCACCCAGACCAGTTTNCATACATAGAAAGTTACAGCTGCTTTTATA CCCCCTTGCCCCGCCAACGTAGTTAAGAGAACAGCAGCATAAGCGGCTGGCAGAGGCAAG GAAAGACCAGTAGAGAAAAAAAAGGCCATCTATACCAATTNTAAGTTAATTTAGACTAA ACAAGGTCTTAATAGCAAAGGATAATTGAAATCCCAAACTTACAAGGTTTTTTAAC Sequence 1390

Sequence 1391

Sequence 1392

TABLE 1 229/467

Sequence 1395

CCGGGCAGGTACAAAAGGGTTCCTCTATATGCCAACTAATTCCAAATTTTTACTTTTACT GCAAAAAAACCTTTTTGGCATCAAAACTCCATTGTTTCTCTGCACTCTGACACCATCATT TCAAAGGGGCTCACATAAATGATCACTACTGCTCTCCCCTAATTTTTGAAAAAGGAGTT TTGAGAATAAAACAGTGCTTTTATTATTAGCCAACACAAAGTGTGAGAAAATCATTCCTG AGAATTAACATTTTAAGCTAACAGAAATTCAGTATACTTAAAACATAATTATATTTAATG AGTCATTATTTGGATCTAAAACGGACGCGTGGGTCGAAGACCTCGGCCGCTCTAGAA Sequence 1396

CCGGGCAGGTACCAGTTTGAGTTGAAACGGTATGTGACTTCCCCAGCTGCGCCCTGGGCA GTGACTGCATCACTCAGAGAGGTCCTGTCTACAGCAGATAAAACTCCACAGATCACTC CTCCTGTAATCCCTCTAAGTGCTCCAAGGCAGCAGAAAGGCCCAGTGCATTGAGGCTGGA AGCAGGAGCAGAGACTCTGGGATATAGTGCGAAAGTCTCTTTCCCCTGTAGTTGGGCTAA TCTGGAAAAACTCAAAAACCTGGCCTGATTACCGAGGTTTCTTTTATGGATATTTAGTAT TTAGATAAAATTTTTACAGTATTCTTGAAATGAACCCAATTAAACACATAGT Sequence 1397

AGGTACTTTAATCCCGTCTTACAGAAGAGAAAACTGAGATTTAGCAACATAAAAGTATTT CCCGTAAGTAAACAGTAGAGCCAAGATCTTGACCTACGCCATCTGATACCTGAGCCCATG CTATAAAAGAGGAGCATTAGAAATATTTGAAAGATAGAAATGAGAACTAGTCAATATTTA TTTTGCTTAGCACTGTATTCAGTATTATGGCATCTTAAAGTAGTTAAGACTCAATATTTC ATCAAAAAAGTTTAAAATCTAATCAGAGAAT

Sequence 1398

TABLE 1 230/467

TTTACCATCTTCATANTTTTTCTTTCCCTTCCCTTCAAAAAAACTNAANTTTTTC
NAAGGTGGAAGAANTTTTTAATTNAANTGGAAAGGGANGCTTCCCTTCTTCCCCAGTTCC
CTTCTTAGCCNATGGGAGGGGAAACCGGG

Sequence 1400

Sequence 1401

CCGGGCAGGTACCAGTTTGAGTTGAAACGGTATGTGACTTCCCCAGCTGCACCCTGGGCA GNGACTGCATCACTGAGAGGTCCTGTCTACAGCAGATAAAACTCCACAGATCACTC CTCCTGTAATCCCTCTAAGTGCTCCAAGGCAGCAGAAAGGCCCAGTGCATTGAGGCTGGA AGCAGGAGCAGAGACTCTGGGATATAGNGCGAAAGTCTCTTTCCCCTGTAGTTGGGCTAA TCTGGAAAAACTCAAAAACCTGGCCTGATTACCGAGGTTTCTTTTATGGATATTTAGTAT TTAGATAAAATNTTTACAGTATTCTTGAAATA

Sequence 1402

Sequence 1403

Sequence 1404

AGGTGTTACTACTCATTACTGGAGGGCACTGTCACAAACTTCTGACTATCCAGAC
TTGAAGCTGGAAGCAAATACAAGTCTGAGGGGCTCTAAGCTGGGAGGTTCTGGCCTCTCC
CTAGCTCTCATGGCTCTACCTCTCTGCTTGAAGCTCCCTGCACTGCACTCCCATTACTC
TGACTGGGGATAGGACCACTGCTGACAGGGCCCCACCTTCAACTTCTTTCATTGCTCCTC
TTTTCAGGAAATCCCCACCCTGGGGATACTTCAAAAGACCT

Sequence 1405

AGGTGATTCAGCAGGTCTGGGGTGGGACTGAGAGCTTGCATCTCTAACAAGCTCCCAGCG AGGCTGATCCTGTTGCTCCAGGGACCACCCTTGAGAACCACTGGTTGGGCATTGATGAG GTCAACCAGGAGAAGCAGTGTCCCCTAGAACTGGCAGGAGAAAAGGACAAGGCTAAGAA ACAGTGAACAGGAGTCAAGTAAATGCAGCTGCCAACAGGCGGGGGTCCTTGAGTTCACAT TCTTGGTTCCAGGTGACGTTTCCTGGGAGTCAACAACCCTTCTCCTATGAAAAAGAAAAG GGCCAGACACAGTGGCACACGGCTGTAACC

Sequence 1406

TABLE 1 231/467

AGGTACTCAATCTAATCCAAAATTTTCTTTAGCAATCTATTTTCTGTATTTAGAAAA
ATGTTTTTTATTTCAAAGAGCCTCTCAAAGAGCCATTTCACGTATCTTTTACTGTTTTTCT
CTCCACCTCCAAGGGGTCTGTCTAGATCAGTGCGGACGCGTGGGTCGAAGACCTGCCCGG
GCGGCCGGCCGCCCGGGCAGGTACTGAGGACAAATCAGTTCTCTGTGACCAGACATGAGA
AGGTTGCCAATGGGCTGTTGGGCGACCAAGGCCTTCCCGGAGTCTTCGTCCTCTATGAGC
TCTCGCCCATGATGGTGAAGCTGACGGAGAAGCACAGGTCCTTCACCCACTT
Sequence 1408

AGGTACATATCACACATTTCCAAATTTGAGACCACTAATGTTTTTTAATTTCAAATATGT
ATATAAATATGTATTCTTATTTCCAATTATTTCCTTGGCATGAATTCCTAGAAATTGATC
TATTTAGTATAAGTGCTTTTTTAGCTATATGTCCACTAGTATGGTATGAGAATGCCCTGT
TTATGCCAGTATTATCATCATTGAATATATTACTGCTGATGTTGTGGTAATACATTTAAA
CCAATGTGATGGGGCAAAAAAATTATATTTTTTACTTACATCTTTAAAATTACTGGNGATC
TCTGNTATTGACAAGCTGGGCATANAAAAAGTAAATTAATAGAATT
Sequence 1409

AGGTGATTCAGCAGGTCTGGGGTGGGACTGAGAGCTTGCATCTCTAACAAGCTCCCAGCG AGGCTGATCCTGTTGCTCCAGGGACCACCCTTGAGAACCACTGGTTGGGCATTGATGAG GTCAACCAGGAGAAGCAGTGTCCCCTAGAACTGGCAGGAGAAAAGGACAAGGCTAAGAA ACAGTGAACAGGAGTCAAGTAAATGCAGCTGCCAACAGGCGGGGGTCCTTGAGTTCACAT TCTTGGTTCCAGGTGACGTTTCCTGGGAGTCAACAACCCTTCTCCTATGAAAAAGAAA Sequence 1412

AGGTCAAGCTTCGNTCCACGCGTCCGGGAAAAACGGGGTTACTAGTAGCCGCCCATAGCC TGCAACCTTTGCACTCCACTGTGCAATGCTGGCCCTGCACGCTGGGGGCTGTTNGCCCCT GGCCCCCTTTGGTTCCTGGCCCCTTAAANAACAGGCNGGTTTTATTAAACCCCAANNNN CCCGGNTTANAAGGGGAATTNAAAAAAGGGCCCCGGCTTTNGNAAAAAAAAA Sequence 1414

NCNGNCCAGGTCTACTCAAGTAGTCTTTACCCCCTACTCAAGTAGGGGGTAAAGNGTAGA ACANGGAGTTTTGATCTGTGTTCAACATGATTGCGAACCATCAATTGAGATAACTCACTA CCTTCAGGCCAGCCAGNTACATACTTTTGAAAAGCCAAGAGTGAAGCANGGTTGATNTTC ATCCAATTCTTGNNCTTTTTGTTAAAGGCANNAATAAGANAGGGTGGNTNCGGGCAATCA CTTAGCTAA

TABLE 1 232/467

Sequence 1415

Sequence 1417

Sequence 1419

CCGCGGTGGCGCCCCGGGCAGGTACATCACCCTGCTGAGGGACATCCAGGACAAGGT CACCACACTCTACAGAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTCACCAA CTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTGGACCC CAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTGGCTGGG CTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATCAGTTTATCAACC AACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCAACCTACCATA TTCCCAGGACAAAGCCCAGCCAGCCACCCAATTACCAGAGGAACAAAAGGAATATTGA GGATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGTTATT Sequence 1420

CCGCGGTGGCGGCCGAGGTACACTGTAAATAGCCTTTACCAAACGTGTTTGACAAGGACC
ATAATTAACATCACTTAGTGAATTGTGATAAAGAAAAAAAGCCATGATTTATTCGATGT
GATTGGCTTGTTTTTATGTGGCGCCAAGAACGAACCTGTTTAGCAGCTGTAACCAATGGT
ACGCGGGGAGCGAACAATGGCGGAGCTGGGCGAAGCCGATGAAGCGAGTTGCAGCGC
CTGGTGGCCGCCGAGCAGCAGAAGGCGCAGTTTACTGCACAGGTGCATCACTTCATGGAG
TTATGTTGGGATAAATGTGTGGAGAAAGCCAGGGAATCGCCTAGACTCTCGCACTGAAAAT

TABLE 1 233/467

TGTCTCCAGCTGTGAGACCGCTTCATTGACACCACTCTTGCCATCACCAGTCGGTTTGCCCAGATTGTACCTGCCCCGGCCGCTCTAGAACTA

Sequence 1421

Sequence 1422

CGGGCAGGTACGATGGGAGGACAGCTTTGTAGAAAGGACATTATCCAGCTAATAGCAAAC TTTGTGGATCCCAATCCGAGATTTCCCTTGCTGAAAGACAAGAAAGTATCTCATATAAAA GTGCTGTAGCAAGTATTTGTATACTCCAGAAATAAGCTTCTGTAATTCTTAGCTGCCAAT GTGTTCAGGCGTGATGACTCGGTTTCTGTTTCTCTGAACATCAATACTAGGGTCTGTATA ATTTCAATGCATGCCACCAGCTTCATCAACCCTT

Sequence 1423

AGGTACAATCAGAATGCTGCATTCTCCAGCCATAAAGATCGCTCCCTCTTCTTTTCAAAC
ATCCCTGTCCCTCAAGGTCTAGCTCAAGACGGTCACCTTAAGAAAAGCTCCCTTTGTCGA
GCAGTGACTCCATACCAGGCCCTGCTTTAAACGCTTTATCTGCATTATCTTACTTGATTC
TCGCAATAGCCCTGGGTGGTAGGTGCAATTATTATCTCCAGTTTATAAAAGAAGATACTG
AGGGTCAGAGAAGTTAAGTGACCGGCTCAAGGTGTCACATTCAGTAAGCGTTGAAGGGGC
CTGTGTTGGTCTGTCCTTGAAGATGCCCCCCTACCGACTACACTTTCAATGATTTTCTGCC
TTGAACCTGGCCCCATGACTAAA

Sequence 1424

NNCAAACCTCCTATGCTTTCCTTGGCATCGGCTACACATCATAGTATTCATTGCCTCCTT GAGGTCATCTTGCAGCTTGGACAGAAACTCATTTACTGACCGGCTCAGCTCATTCTCTGC CATTCGTTTCATCTCATACTCCTTTCGCTTTTCAGCATTGCTGACAATGTCCCAAGCTGC TCGCAAAACCTTGAAGGCCTCCTCAGCCCGGGGATGATGATTTTTGTCAGGATGAACCAT CACTGCCAGCTGTCTATAG

Sequence 1425

Sequence 1426

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTTGGGCCAAGGCTGCAAT CAGTGATTCAGCCGACTGCTCTTTGAGTCCAGATGTTGATCCAGTTCTTGCTTTTCAACG AGAAGGATTTGGACGTCAGAGTATGTCAGAAAAACGCACAAAGCAATTTTCAGATGCCAG TCAATTGGATTTCGTTAAAACACGAAAATCAAAAAGCATGGATTTAGGTATAGCTGACGA GACTAAACTCAATACAGTGGATGACCAGAAAGCAGGTTCTCCCAGCAGAGATGTGGGTCC TTCCCTGGGTCTGAAGAAGTCAAGCTCGTTGGAGAGTCTGCAGACCGCAGTTGCCGAGGT GACTTTGAATGGGGATATTCCTTTCCATCGTCCA

AATTGGAGCTCNCCGCGGTGGCGGCCGAGGTACATCACCCTGCTGAGGGACATCCAGGAC

TABLE 1 234/467

AAGGTCACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTC ACCAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTG GACCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTTGG CTGGGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATCAGTTTAT CAACCAACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCAACCTA CCATATTCCCAGGACAAAAGCCCAGCCAGGCACCACCAATTACCAGAGGAACAAAAGGAAT ATTGAGGATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGTTATTTTTCTGAC TGTCAAGTTTCAACATTCAGGGTCTGTCCCCAACAGGCACCAC

Sequence 1428

Sequence 1429

Sequence 1430

Sequence 1431

Sequence 1432

TABLE 1 235/467

GNAATGGTTTTNTGGNNAAAAAGCCCATGGAAATACTGAGCCCATGCCNCTCACGTTGNA AAAGCCCCGTTCCTTGCC

Sequence 1434

AGCTCCCGCGGTGGCGTAACTTATCTCATTTTAGATNAGTTTGCAAAGAGAGTTTGGTGGCTAAGGCCATAGCTTAGCCTCCTGACCCCTACCTTCCCACGTTCTTTCCAAGAGATTCTCCTAAGGCCATAGCCTTAGCCTTCCCACGTTCTTTCCAAGAGATTCTCCTCAGGAATAACACTTGCAAGGGAGTTCCTGATGAAGTGGATTCTTGTTATTCTAGGAATAGCCTACATGGTGCACTGGCAATGTGAGATTATACCTCAGCATTTTCAAAGAGCATAAAAAAATCTAGAGCTGGGGGGGTTTAAAACATGACAAACCTAATTTTAAGTAGGCAGACCAAATATTTAAATTTTCCCCTACCCTTGTTTCTACATCGGTCCATTCAGACTCTGCACCATCTGGTTTTAAAGTTTCAATCACCCCTTCATTTAAATATCACCCCTTAATTAGTTTAAATTTCAATCTCCCCATCGGAGGCTAGTTCCTGGTGGTCAGCATGTACCTGCCCNGGCNGGCCGTCTANAACTAAGTGGATCCCC

Sequence 1435

Sequence 1437

CTACTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTGCCAGGC
ATGCTCCTGCCTTGGGCAGAGTGTATATGTGTGAGTGCACCTGCCCTTCCCACAGCCTAG
AACGTTCCTCCCAGACAGCACATATGGCCTGCTCTCTCACTTCCTTAAGGTCTTTATT
CAAAAGTGACTTTCTCAGTGAAGCCCTGTCTGCTCACCCTGCGTAAAATTTCAGCTCTTC
TTTCTATCTCTCTCCCAGATTTTTTTTCTCCTTCATGTTCGTTGGTGTCTAAGGTTTAT
CATCTATTTCGCTAATGGTCAGTAGAATGTAACCTCCACGTAAGCAAGGAGTTTTGTCTG
TTTTGTTCATGTCTTAGTCCTTAGTGCCTGGAGCATTCCCTAGTATGCAGTAGGTGCTCA
ATAAATGTCAGTTGGATTAATGGCTGAAAGAAAGGTCACCGCTATAAGGATGGAGTCAGA
GAACAAACACAGTTAATTCCTGGTCCACTGTTTTTTGCTTCACTAAATTGTATTTGGTCT
ACGGCTTCTCCGCTTGCCCTGGAACCCTGCTCAGAACACTGCTCCCTTCTCCTTCTTCTT

TABLE 1 236/467

CTCCCTCCGGATAAATTCT

Sequence 1439

Sequence 1440

Sequence 1441

Sequence 1442

CTATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACAAAGACCAAT TCCTTCCTAACCTGGATTCCACTGTCCTTGGTGAAAACTACTTTGATGGAACCTACCAGA TGCTTTATCTTTTGGTTAAAGGAACTATACCTGTNGAAATTCACACTGCCACAGNGATAT TTGTTTCCAATTATNTGTTGCAACANAAGATGACTTTTATACCTCTCACAATCTGG NTAAAAATCTTGCCTTGTTCCTAAAGATACCAAGTGACAAAATCCGTATCAGCAAAATAA GAGGGAAGAGTCTGAGGAGGAAGAGATCCATGGGATTCATAATTGAAATAGAGATTGGAG ACCCTCCTATTCAGTTCATAAGCAATGGCACCACAGGTCAGATGCAGTTATCTGAACTCC AGGAANTTGCTGGTTCTTTGGACAAGCTGTNATTTTAGGAAA

TABLE 1 237/467

Sequence 1445

Sequence 1446

GGCGAATTGGAGCTCCCCGCGGTGGCGGCCGCCCGGGCAGGTACTCTTAATCCAAGACAA
AAGAATAGCTCCTTTCAGAGTTCTCATCATTTCTTCACCCCAGCCTTAATGGGTATATTC
CTTTTCCCCAGGTGTCCAGAGTTTTCCAGAATTGTCCCAAGGCTCAGTCCACCACCAGTTC
TTCTCCAGTGTGCTCTCCTGAGAGGCCAGGCACACTCAACAATTATCTAGATGAGTTCCC
ACTTCTTTCCAAGTGAAGGTTCTGCTATCCTAGCATAGTCAGAATAAGTTAAATTATGTC
TCTTAAGAGGCACTGTTCCACTCCTTTTCAAGGNGTGTGGCATATTTGAAATATGTGACT
TAAAAGTCTACAGTCTCTTACCAAAAGCCTTGGGCCAAATACATGTCAAAATTCAGAATT
TTNCAGATTTTAGAAAAGTGACCCATATACCATACATTGCA

Sequence 1447

ATAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACATCACCCTGCTGAGGGACA
TCCAGGACAAGGTCACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCT
GCCTGGTCACCAACTTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCT
CCAATTTGGACCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCAT
TCCATTGGCTGGGCTCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCAT
CAGTTTATCAACCAACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCA
CCAACCTACCATATTCCCAGGACAAAGCCCAGCCACGCACCACAATTACCAGAGGAACA
AAAGGAATATTGAGGATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGTTATT
TTTCTGAC

Sequence 1448

Sequence 1449

CCGCGGTGGCGCCGGGCAGGTACATCACCCTGCTGAGGGACATCCAGGACAAGGTC
ACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTCACCAAC
TTGACGATGGACTCCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTGGACCCC
AGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTGGCTGGGC
TCCACCTACCAGTTGGTGGACATCCATGTGACAGAAATGGAGTCATCAGTTTATCAACCA
ACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCATACT
TCCCAGGACAAAGCCCAGCCAGGCACCACCAATTACCAGAGGAACAAAAGGAATATTGAG
GATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGTTATT
Sequence 1450

CCGCGGTGGCCGAGGTACAAATTGNCGTTTTTATTCCTCTTATTGGGATATCATTTT

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Sequence 1451

CCCCGCGGTGGCGCCGNGGNACAAATTGTCGNTNNTATTCCTCTTATTGGGATATCATN
TTAAAAACTTTATTGGGTTNTTATTGTTGNTGTGGGNTCCCTAACCCTACAAAGAGCCTT
CCTATTCCCCTCGCTGNTGGAGCAAACCATTATACCTTACTTCCAGCAAGCAAAGTGCTT
TGACTNCTTGCTTCAGTCATCAGCCAGCAAGAGGGAACAAACTGGTCTTTNNCATTTTG
CCNCTGNGATATGNCATTGCACTGCTTATATGCCAAGCTAATTTATAGCAAGATATTGAN
CAAATATNGAAAGTTGNTATTCAACCTCACANGGGCTCTCAAAGTATAAATCTTTCTATAG
CCAACTGCTAATGCAAAATTAAAACATATTTCATTNTAACATGATTTCAAAATCAGATTTT
CATACTACCCTTTGCTGGAAGAAACTAAAAATAT

Sequence 1452

Sequence 1453

Sequence 1455

CGAGGTACTGACCTCGTNTGTCCCTTCCCCTNCACCGNTCCCCACAGCTTTGCACCCCTT

TABLE 1 239/467

Sequence 1457

Sequence 1458

AGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCCGCCCGGCAGGTACTGGAACAGGGATAA
GTTCTTGGATAAGGNGCCAACATACCTATAAAAGCTGATTTTTGAGTAAATTATTGATTC
TAACATATGTAATGGATTTGGTGTGATAATTTTCTGATCTTTAACTATAAGTGACTTTTT
ATTCTCCACCAGAAAAGATAAATGACTGAGAATGTAAGTCTGCGCTCTGATTAACACAAT
GGAGAAACGGAAAAACTATCTCTGTTAAAAACTGATTCCTGTCATTCTTCTGATATCAAA
TAAGAGGAAGGAAAATAAACTTTTTGTGTGTAGATAGAAAAAACATACCTGAGGCCAGGTG
CAGTGGATCACGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGCGGGCAGATCAGCTGAG
GTCAGGAGTTCGAGACCAGCCTGGCCAACATGGNGAAATCACGTCTCTACTAAAAATACA

Sequence 1459

Sequence 1460



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AGGTACGCGGGGCTCAAGAATAAGCTGAAATATGGCCAGACTATCAGGCCCATTTGTCTC
CCCTGCACCGAGGGAACAACTCGAGCCTTTGAGGGCTTCCTCCAANCCTACCCACTTTGG
CCCAGTCANACCAAAAAAGGGGAAAGNAGGCCTGGCTTCCCCTTGNCAACAAGGGNATTA
ATTCCAAAAAGNCCTTCCTGGTTTTTTGGNTGGTNCCTTGAAGGGNAAGGGNAGGAAAAA
AAAAGNCCTTGNAACCTTCGGGGAAGGGGNAGGGTTCCTTAACAATTCAAAAGGAAATTG
GGGGGGGGAATAAAAGGAAAAANGGGGCCAAGNCCTTGGTTTGGAAGGAAGGNAGGTATG
GCTTCAAATTAATGGCCCCCCAANGGCTTAATTGAACCAAAAAAGGGTNCAAAAGGGGAA
CAATTCTTCAANAAGGGTTGGGGTTCCACCCCCCCNTTCGGGGTTTTCCCCTTTTTTGGTT
ACCCCTTGGCCCCCGGNNNCCGGGCCCNGCCTTCCTAAGAAANCNTAGGGTTGGGGNANT
NCCCCCCCCNGGG

Sequence 1462

Sequence 1463

Sequence 1464

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AAAGGNNTTGGGGGGNAATTTCCCCCCCCCCCGG

Sequence 1465

Sequence 1466

Sequence 1467

Sequence 1469

CCGGGCAGGTACTTTTTTTTTTTTTTTTTTTTAACTGAAGCTTTATCTGGAGTGGGGAA TGGGGGTGTGGTCAGTTGGGGCACCCAAAGNACAACTCATGCCTCCTNCNNNGAAAGGNC GGCCCAAGGGTCCCTGGGCCAATTTGGTTTTCNTGGGATTTCTTCTTTTTCGGNTACATCG GGNCAATTTTCCGNTACACCTNCNCCTNCNAAGGGNCCCNAGGTNTGGCTTTCNCNNCGC GCAANAGNTNGTNCCCTTTTCACCCGGAATGGAATGGTTAAGACCTTGNAAGNGGATTTT GGGNGGACCTTTTNCATTANCTTACCCCCCCCAANGTAAAAAAATTTCCGGTNNTAAGGG

TABLE 1 242/467

GNAAGAAAAGGAACCCNCCCAACAATTGAAGGNGGTTAAGGTTGGGTATTTTCCTTTTCC
TTTCCCCCTTTCCCCAAAGGCCNTTTTTCNAAGGGGGGGGCCTTTTTNCTTTCATTAACC
AACCTTTTTGGNAATTGGGGGGGGGGNCCTTGGGAATTGGGAAAAAACCGGTTTNCCCGG
CCTTTNTCTTTGNGTTCNCCAAAAACCCCCTTGGGCCAAACC

Sequence 1470

Sequence 1471

Sequence 1473

TABLE 1 243/467

CCCAGCCCGCNTGCTTCACNTTTCCACCNCTTTTNTTTCTCACCTTGCCTTCTTGGGCT
TTTCTNCAAGGGCCCCTNNTGGCCTTTCTTCCCCGNACCCCTTTGGTTCTTCNCTTCTGG
AAANAACCCNCTTCNCTNCCAACCAAACCTNNGCAGNCTCCCATTNNCTTTCCCCGGGCT
TCCCCCNTCNCCTTAAGGTTCTTGGTTCCCCTTGGCCGGTTCNCCTTCTTGGTTCCCCCG
GGGTTTTCAAGNAGNAACAAANCNTTNCCCCAAAAANGCCAACAAAAAAGGCCAAGGTT
TTTTTTTTCCCCCCCCTTTAAAAGNGGGNNTGGGGGGGAAGGGGGAAAAAACCTAAGGGTG
GGGAACTTCTTGGTACCCCTTTTTNGGGGCCCCGGGCTTCTTAAAGAAAACCTAAGGGTG
GGGGAAATNCCCCCCCCCCG

Sequence 1475

Sequence 1476

Sequence 1477

Sequence 1478

AGGTACCTTAACTTGAGTTACAGGGCTGGTCCCTCTCTTTTCATTTTTTATCCCAGTAGG
TGAGACCGTCCCTGCTGTGTCGGTGGCTGTGGAGTTGATGGCATCTTTGCTCCAGGTGA
CACCTGCATGCTGGCCAGCTGAGCGGCATAGAGCTGCCAAAACAGGGAAGACAACAT
TGATCTCTTTAAATGCAGCTGAAATTGAGTTTCAAAAGAAAAAACTTACCATATTGTTAG
ATTTCTCAGACAGCCTTGTAATTTCTTTTTCACTATTTTTAAAAAAGGGAGCTAAGAGAA
GGCAAATAATAAAAACAGAAAGAAAAAGGACAGGTATGGGAGCCATAGTTCTGTTTCTGGT
CCTTCTAGCAACAACTTTATGATCCTGGACAAAGGATTTGATCTCTTTAGAATTCAAGTT
TTTTTTTTA

Sequence 1479

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Sequence 1480

Sequence 1481

ATTGGAGCTCCCGCGGTGGCGGCCGAGGTACATGATTGTCCTTTATGCATTAAATTCAT
GCTTTTACATACTTGTGTTTCCTTTTCATTTCGTCCTTCCAAATCATTATTTTAGGAATA
TAGAGAAAAGGGTTGGCCAGGTGCAGTGACTCACACCTGCAATCCCAGCACTTTGGGAGG
TCGAGGTGGGTGGATCACTTGAGGCTAGGATTTTGAGACCAGCCTGACCAACATGGAGAA
ACCCCATCTCTACTGAAAATACAAAATTACCCGGGTGTGGTGGCGCATGCCTGTAACCTC
AGCTACTCGGGAGGCTGAGGCAAAAGAATTGCTTGAATCTGGGAGGCGGAGGTTGTGGTG
AGCCAAGATCGTGCCATTGCACTCCAGCCTGGGCAACAAGAGCGAAACTCCGTCTCAAAA
AAATTAAATAAATAAGGCTTATGTGCAGTTATTCTCAATGAGCTAAAAAAGCTTCCTGAGG
CTAGAAATTCTTGTCATTTTTGGCTGGGA

Sequence 1482

GCTGCCATCAGCTCCCTAGGAGCTCTCCCTCCAGGAAGGGAATGTGTCCACCGTCAGACA CTCAGACCCAGCATGTGGGGACAGAGGCTGATGGCCTGTCTGGCCATTCCTCTCAGTTCC TCTCCTCACTAGCTTGTGCCTTGTGCAAGTCACTTACCCTCTCTGAGGTTCAGTTCCCT CCTCTTTGAAGTGGGTTTAATAATAAGTACCTGCCG

Sequence 1484

CCGCGGTGGCGCCCCGGGCAGGTACTGCCCTTTCGTTAGAAGGCAGTGACTCCTTTC
TGTGAAGCCGATTTAGTGAAGTGTCCTGTGCAGAAAAGAGTCCAGGGCTGTCAGTTAATT
TCTTCCGGCCACTGGAGTTAGGGTTTGAAACTCTGCAGCTGCCTATTGCACTTGTGAAAA
GGTTTGTATGTTCATCACTGCTGGCTGGCTCAGAGTTGGGAGTGAATCCTCCAAGGGATA
AGCTTGGAGAACTTTCTGAACAGTCAATCTGTAAAGGTGTCTGCAATCCCAAGGCCAATG
GACTAGATTCTGAAGGCTCTCGGTGGACCCACTGTTCCTCTGTTTATTAAGCTTTTTG
AAGGAGAGAGAGAGAGAGACATGTGACAACGGTGCTTTTCCTTATGCTTATATCGCT
CTCCAACAGCATCCTT

Sequence 1485

AGGTACATGCAAGTTGCATGATTATAATGACGTGATCCTGGGATTTAAGTTGATTATGAC
AGGAACAGAAGGAACTTGGAGATTAGGGACAATGAAAAGGTGGTAGTGAAAGGAGTGTTG
GAGTTAAGTTACTAGATGTCTGGAAGACAGACTGTGGTGGTCAGATAATGAGATAATGAGATTA
TGGAGGGGTTACAGTTTTTGGTAATAACGAGAGAGTCTAAGGTATGACTGAGAGTGAAT
GGATGAGAATAGCAGAGAACAAGGTCAGTGGAAAACTACTCTTCAAAGAACCTATAGTCA
GGGTGTTGAAAGATTAAAAATTGCTAAGAATTAAATCAGGAAGTAGTGCTGCGGGAAATG
AAATGAGCAGTGAACTAAACTTACTGAGAAATGAGAGGGGATGACCCAAGGGTTTGTAGA
TTTTGTAGATGATAGCA

Sequence 1486

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AGGTACATGACATCCGACGAAATGAGACGCCACCTAATTGATTTCCGGGAGTCCGCACCA GGGGCCCTCAGGGAAGACCCCGCAAAGATCCTGGGAGACCAAGGTGGGGACCCTGGTG AGAAGAGAGAGTTCAGGGGAGTCTCTCTTCATTGCCCTTCTGCTAACCCAAGCATTAATT TGCTAAGTATTTACCAGGGGAGTGGGAAAAAGAGTTGAGCGGGATTCTCTTAGGCTATGA GAGAGTCAGGCAGCCCCCAAGATAAAATAATGAACTAGAAAATCTGGAACCTTACTTCTC TGGGAATNTTACCTATCTGGCACCGTGGGAAGAAAAAAAAGGCTACTGAGTACCTGCC CG

Sequence 1487

GCGGTGCCGAGGTACTGACCTCTGCCAGTCAGCTGCGTAACTCCAGGCCCTAGGGT GCCCGTCTGTCCAGCCAGGGATTGCATGGATATGCTGTGATCTCCCTTTTGGTTCTGAT TGAGTTGGACCTTGTGGGAGGAGAAACATAGATGTTGATACATGAACACATATGTTGGAG AGAGAAAGTTTATCTTGGCATAGGACTTTTAAAACACAAGGTAATTTTTAATCAGTTTT GGGACCAAAAAACACTCAATATGGGAAAAATCCAAATTCTGCCAAAATGTCTAAAGAGGT TTATTCTGAACCAGTATAAGTGACTGTGGTCTAGGTTACACAATTTCAAGAGATCCTGAT AAAGCGTGCATGAGAGAGTTGGGCTACAGCTTGGTTTTACACATTTCAGGGAGACAGGAA TTGTANGGTAAAATTATGGCACAGGACTTTTAAAATGAAGCTGTGAAAGTTTACAGTCCA TAGAGAATAAAAATCTAGAAGTTT

Sequence 1488

Sequence 1489

GGGCGAATTGGAGCTCCCCGNGGTGGCGGCCGGGCAGGTACCCAGAGTTGCGAGGAGTTT
TTTAACTGATTTAGCCAGGTGGCAANCATNAGTGAATGGATGAAGAAAGGCCCCTTAGAA
TGGCAAGATTACATTTACAAAGAGGTCCGAGTGACAGCCAGTGAGAAGAATGAGTATAAA
GGATGGGTTTTAACTACAGACCCAGTCTCTGCCAATATTGTCCTTGTGAACTTCCTTGAA
GATGGCAGCATGTCTGTGACCGGAATTATGGGACATGCTGTGCAGACTGTTGAAACTATG

Sequence 1490

Sequence 1491

CTTAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCTGGTGACCCTTGCTGGT GCTTTCATGTTTTGTGCCGAGGCAATTAGACTTTGTGCTGAATNTGTTTTGTGCTGCCACC TCAGGGAAGGGGTGGAATGTGCAGCGTGGTTTCCATTTGACATTGTTTTCCCTGAGAGAT GGGAGGGCTGAACGTTACCTCTTGACAAGTCTTAGTGGACAGAGGGGCCCGGATACCCAA GCGCCTTAGTTCTTAGGGCTGGGTATTAGTTCATTTTCACACTGCTGATAAAGACATACT CGATACTGGGAAGAAAAAGAGGTTTAATTGGACTCCCACATGGCT Sequence 1492

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Sequence 1493

Sequence 1494

ATAGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTAATTTGAATTTGTAATGA
GTCTGATGGTATATTTCAATTTTTTGCTTTGAGGGACTGGCTGCTACATTGCAGAATATC
TTATATCCCTGACTGCTTTCCACTAAATGTCAGTGGTGACCCCAATCCAATTATTATGAC
AACTGAACATGCTTATGCATCCCTCATGCCTTTATTTTTTATTTTGGGAAATCTTTCAGC
TTCAGTTTTTGCTGATATTTATGTGATTCTTTGTTCTGCAATTCAAATTTCTGGGAGCCA
AACAGTCTCCTTGGTTCAGATTACTGTTTTTTTGACTAGAGCTTCTCGCTTCAGATTCTGT
CATAAGATTATGGCTTAACCTATGGTTGTCCTTTGATTTGGTGCCATATGAAATAAAACA
TTATTT

Sequence 1495

Sequence 1496

CGGGCAGGACCATGGGAAATAAGAGCNGGCTNNNGGCATTCTGNGTANGGAGCCTGAGCC
AAACTCTAAAGCTGTCTTTATAAAGGGAGGTCATGTGATGGCCAGAAATTGCCTTTGCTT
CATGGTGCACTTGGTGGGGAGTCAGGTGTGGGGTGTTCACATCATCCCATTTTC
TTTTNNGNNTTCAGACCTGCAATGCTTCTTTTGCAACCCGAGACCGTCTGCGCTCCCACC
TGGCCTGTCATGAAGACAAGGTGCCCTGCCAGGTGTGTGGGAAGTACCT
Sequence 1497



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Sequence 1499

Sequence 1500

Sequence 1501

CACTACTATAGGGCGAATTGGAGCTCNCCGCGGTGGCCGCCCGGGCAGGTACGCGG
GGGCCACTGACCACAGCTCTTTCTTCAGGGACAGACATGCTCAGCGGATGACAACACAG
CTGCTGCTCCTTCTAGTGTGGGTGGCTGTAGTAGGGGAGGCTCAGACAAGGATTGCATGG
GCCAGGACTGAGCTTNTNAATGTNTGCATGACCCCCAAGCCCCACANGGAAAACCCCGCC
CCCGNGGACAATTTGTTTTNACCANGTTTCCCCCNTTGGNNNNAAAAAATTCCTTTTTT
TTTNCCNNCCCCCCCCCGGGGNGNCCCCNAAGGGGGNNTTTTCCCCNNTTTTTTNANTNNC
CCCCCCCCCCCCCGGGGGNGGGGNGNCCCCCCTTTTTNNNAANNANTTTTTTTTN
TNNAAAAANCCNCNNNTTTTTTANAANGGGGNTCCCCCNNAATNTNGGGGCCCNTTATCC
CCNGGGGGNTAAAANAAANTNTTNNCCAAAAAGGGGGGNCCCCCTCCCCCTTTTTNAAAA
NAGGGGGCCCCCCCCGNGGGGGGNNGNGAANTNATAAAANTTTTTTTTCNCCCCCCC
Sequence 1502

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CNTCTTNTTTATAAAANAAAAAA

Sequence 1503

Sequence 1504

Sequence 1508

Sequence 1509

CCGCGGTGGCGGCCGAGGTACGCGGGAGAACAGCTCAGAAGGAGACCCACAGTGAGCAGC TCCCCTGTGTCGGCGGGCAGGTCGTCCCTCAAGTGTTCAGCTCTCAGCAGAGAAAAGGCC CTGGAGAGGGTGACTCCTCCAGCTCTCAGCAGAGAAGCAGCCCTGGAGAAGGTAGCTTC TGTTCGCAGGCAGATTGTCCAGAGGTCCTGCTGCTCTCAGACGGGGCCCTGGAGAGGATA GCTTCTATCCATAGGCAGG

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CCGCGGTGGCGCCCCGGGCAGGTACGCGGGGACAGAAATGGAGTCATCAGTTTATCA
ACCAACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCAACCTACC
ATATTCCCAGGACAAAGCCCAGCCAGGCACCACCAATTACCAGAGGAACAAAAGGAATAT
TGAGGATGCGCTCAACCAACTCTTCCGAAACAGCACCACACCCGGGGGTGGACTCCCTGT
TCAAGTTTCAACATTCAGGTCTGTCCCAACAGGCACCACCCCGGGGGTGGACTCCCTGT
GTAACTTCTCGCCACTGGCTCGGAGAGTAGACAGAGTTGCCATCTATGAGGGAATTTCTG
CGGATGACCGGAAATGGGTACCTCGGCCGCTCTANAACTAGGTGGGATCCCCCCGGGCTG
NAAGGAATTTCGATATCNAGCTTATCGATACCCGTCCGACCCTCGAGGGGGGGGCCCGG
GTCCCAGCTTTTTGGTCC

Sequence 1513

Sequence 1510

ACTACTTAGGGCGAATTGGAGCTCCCGGGGTGGCGGCGAGGTACGCGGGAGGCCAAGC

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Sequence 1516

Sequence 1517

Sequence 1518

Sequence 1520

Sequence 1521

CCGCGGTGGCGGCCCCGGGCAGGTACATCACCCTGCTGAGGGACATCCAGGACAAGGT

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CACCACACTCTACAAAGGCAGTCAACTACATGACACATTCCGCTTCTGCCTGGTCACCAA
CTTGACGATGGACTCCGTGTCGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTGGACCC
CAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTGAATGCCTCATTCCATTGGCTGGG
CTCCACCTACCAGTTGGTGGACATCCATGTGGCAGAAATGGAGTCATCAGTTTATCAACC
AACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCACCATCACCAACCTACCATA
TTCCCAGGACAAAGCCCAGCCAGCACCCCAATTACCAGAGGAACAAAAGGAATATTGA
GGATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGT
Sequence 1522

Sequence 1523

Sequence 1524

Sequence 1525

CCGCGGTGGCGCCCGGGCAGGGTACACCACTGTGCCTGCTTTGAATCCTTTACGAA GAGAAAAAAAAATTAAAGAAAGCCTTTAGATTTATCCAATGTTTACTACTGGGATTGCTT AAAGTGAGGCCCCTCCAACACCAGGGGGTTAATTCCTGTGATTGTGAAAGGGGCTACTTC CAAGGCATCTTCATGCAGGCAGCCCTTTG

Sequence 1526

Sequence 1527

TAGGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACCTGTGGATATTGGTTGAACA
AACAGGTGGGCAAAGTGAGGAAGATAAGAAGTCCATCCGTTCAGTTTCCCCACTGCGGAG
GGAATAACACTGTCTTTCCACAGGTCACAGACTGGGATGAGCAACGGGCTGAAGGCACGT
TTCCCGGGAAGATCTGAACTGGCTGCATCTCCCTTTCCTCTGTCCTCCATCCTTCTCCCA

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AGATGGTGAAGGGGGACCTGGTNCTG

Sequence 1528

AGGTACGCGGGATGGCACATANGACATCAGCTAGGCTTTTGGGAATCGTTTGTGTTCTTT GTGGAAATGTCCTTTAGAAGCACCCATGAAGTAGTGTGTCAGACTGTGCACACAGAAAA CAGGCTCTGCCTTCACATGTGAGACGGTGGACTTTTCCTNTGGACAAAATGACAGCATNC TGGCGACTCCACAGTGGAGCTGAGCGCCACTCCCTGTAGCCCGATCTGGGACTGAAACGC TTACACCTCTGCCTTAGAAGGAGTCCCCCNTGCC

Sequence 1529

Sequence 1530

Sequence 1532

Sequence 1534

TABLE 1 253/467

GACTITCTTTCCTTGTCTAGGACCAGTTGAAGCTCATTATTAACCTGCTGCAGCTCCTCA CCATTCTCCTCATCGGNGCCTCCATTTACACGAGCAGGGCGTGCCTGCTGCTCACTGTGA TCCAAAATCTCCTNGACTTGCTCAGGGGCATNTGTAGCCTCC

Sequence 1535

Sequence 1537

Sequence 1538

Sequence 1539

Sequence 1540

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GGAGCTAAACCCCGGNGGCGGCCGAGGTACTTACCCTCAATTTCAATGTTAACAATTTCT
TTAAAAAGGCAAAAGACACAAAAGNTTAGCATTTACCAAACCAGTCTGTACGCGGGGCCT
GTGGATGCTGCGCCTCTCCGAACGCAGCATGAAGGTGCTCCTTGCCGCCCCCCTCATCGC
GGGGTCCGNCTTCTTCCTGCTGCCGGGACCTTCT
Sequence 1542

Sequence 1544

GGCGGCGGCCGAGGNACAAGNANCNNTTGGNGGAGGGGGGGGAAACCCAANACCCGAACN NGGGACTGNGCAGACAAGCTATATCTTAANCCCNCNCCGGGCCAGACCNCNAGCAAGGGN GAGGAAGCAAAAGNCCACAGNNACNGGGGCAGGNAANNGGNANAAANGAGGGNGNGGGGC

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Sequence 1547

Sequence 1550

Sequence 1551

GGCGGCCGCTCTAGAACTAGNGGANCCNTTTTGCGGGGGGAAAAAAACCCCAAGCCCANC GANACCGNCGACCNCGAGGGGNNCCCGGNACCCAGCGNNNGCCCCCNAAAGAGAGGGNN AANNGCGCGCNNGGCGNAANCANGGNCANAGCNGNNNCCNGNGNGAAANNGNNANCCGCN CACNTTTTNNTTTNNCNGACGAGCCGGGNGCANAACCCCCAAANANA Sequence 1552

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Sequence 1553

Sequence 1554

ATCGACTNCTATAGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGCCCGGGCAGGTACGC
GGGTGGCCAGATTAATTTTCCAGCCAATAGAGGAAAGTTTTTATATATTTTTTTGCTAAGG
TGCTGGAGAGGGGAAAGGATGCCACACTTCAGAAGCAGGAGGACGTTGCTGTGGCTGCTG
CAGTCTTGGAGCCCCTGCTCAAGCTGGCCCTGCCGGCCTGACCATCACTGTTTTTG
GCTTTGCCTATTCTCAGCTGGCTCTGGATATCTACGGAGGGACCATGCTTAGCTCAGGAT
CCGGTCCTGTTTTGCTGCGTTCCTACTGTCTCTATGTTCTCCTGCTTGCCATCAATGGAG
TGACAGAAGTGTTTCACATTTGCTGCCATGAGCAAAGAGGAGGTCGACAGGTACCT
Sequence 1555

Sequence 1556

ATAGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGTCCACATCCCGAAGGCCATAGCGTC
GAGCAAGGTCACATGGATGGCAGCACCTTACCACTCAGGCTCAGGATATTGGGATCTGTT
GCCAAAGCCACCACCACATTTGCCACTCAATTCTGTGGTTTCCGCAGATGAGAAGGCTGAT
TTGAACTGCTTCAACACAGGATCCTGCAGGACCTCCTCTTTGCCATATGCTCCTTCAGC
AGTTCTGTCTGCACAATCCCCGGCCACAGAGACACACAGCTGACCCCATGGCGCCGCAGC
TCGTGGGCACAGTCAGCAGCTTGTCACACGCAGCTTTGCCCACACCATAGGGGACA
TTGAACATATACTGCAGGCTTCCTGGGGAGGAGATGACCACGATNAGCCCCTGGCCAGCT
GGTACCT

Sequence 1557

Sequence 1558

CCGCGGTGGCGGCCGGGGGCCATTG'AGACTGCCATGGAAGACTTGAAAGGTCACGTAGCT GAGACTTCTGGAGAGACCATTCAAGGCTTCTGGCTCTTGACAAAGATAGACCACTGGAAC CAATGAGGAAGGAGAATTCTACTGGTCACAGACAAGACTCTCTTGATCTGCAAATACG

TABLE 1 257/467

ACTTCATCATGCTGAGTTGTGTGCAGCTGCAGCGGATTCCTCTGAGCGCTGTCTATCGCA TCTGCCTGGGCAAGTTCACCTTCCCTGGGATGTCCCTGGACAAGAGACAAGGAGAAGGCC TTAGGATCTACTGGGGGAGTCCGGAGGAGCAGTCCCTTCTGTCCCGCTGGAACCCATGGT CCACTGAAGTTCCTTATGCTACTTTCACTGAGCATCCTATGAAATACACCAGTGAGAAAT TCCTTGAAATTTGCAAGTTGTCTGGGTTCATG

Sequence 1559

Sequence 1561

CCACTCACTATAGGGCTGAATTGGAGCTCCCCGCGGTGGCGGCCGGAAGAGCAACCGAGA TGAAGGTGAAGATGCTGAGCCGGAATCCGGACAATTATGTCCGCGAAACCAAGTTGGACT TACAGAGAGTTCCAAGAAACTATGATCCTGCTTTACATCCTTTTGAGGTCCCACTGAGAA TATGTAAGAGCTTTAAATGCTACCAAACTGGAACGAGTATTTGCAAAACCATTCCTTGCT TCGCTGGATGGTCACCGTGATGGAGTCAATTGCTTGGCAAAGCATCCAGAGAAGCTGGCT ACTGTCCTTTCTGGGGCGTGTGATGGAGAGGTTAGAATTTGGAATCTAACTCAGCGGAAT TGTATCCGTTACCT

Sequence 1562

GGGCGNGTTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTCTTCCTGCCTTCCCCCATATA CTGAAGTTTGAGAGGCTGGGAAGGTGCGGAATGGGAAAAGGAGCAGCTGCTTATGTTCAG TTTAACATTCTCTGGGTTTCTCCATCTAGGTCTTGAGTTCATTCTCTTCCTGTCCTTTTG GCTTCCTTGTTTAACCTGGTCCCTGTTTCAGGAGAGAAGCCTCATCAGTGCCAAGTCTGT GGGGAAGACCTTCTCTCAGAGTGGAAGCAGGAATGTGCATATGAGAAAGCATCACCTGCA GCTGGGAGCAGCTTGGGAGTCAAGAGCAGGAGCAAACTGCTGAGCCACTAATGGGGCAGT AGTTTGCTTG

Sequence 1563

GGGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTCCTTCGTAAACCATGGAGAGC
CAGCCCAATGCACAGCAGTGGATATCATCTTTCTCAGAGTCCAGTATCACAGAATCACGA
CTTTGTCCAGCTGCAGGTGCCTGCAGGTCACACTGGCTAACTACTTTGTGATGGGCTCTT
CTTTCTGAGGTTCTGCCAACTTGTCTACTACATAGGGTTGATCATCCTGTTCAGGAAATA
TTTCTTTCATTTGCTCTGAGCTTAATATTGTAATTTGTATTTGATCTGCTGGGTCTTTGG
AGTCAGGACTGGTTTTATCAGCAGTTTGATCTTCTGAGGTCTGGTATGTAGTTTGCTGGC
CCACAGAACCTTCACGTGTATTCACAGCCTCAATGCCATAAGGAAACTCTTTTAGAAGTT
CTGACAGCTGGTCATGTAGGTATAAGACAGGTGCCTTATCACTGTGGATTTCATTTCTTG
Sequence 1564

CCGCGGTGGCGGCCGAGGTACAAATTGTCGTTTTTATTCCTCTTATTGGGATATCATTTT AAAAACTTTATTGGGTTTTTATTGTTGTTGTTTGATCCCTAACCCTACAAAGAGCCTTCC

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Sequence 1565

Sequence 1567

TCGCCNCGCGTCCGGGCAACTGCAGTTGGAAAAAAAGATTCAACTTCAAAGCAGAGGATT
TTTGATGAAGAACCAGCTAATGGAGTGAAGATAGAAAGGTTTACAAGGGATGATCCTTGG
TTATCTTCATGTGAAGAAGTGGATGATTGTAAAGACCAGTTGGAGAAGCAACAGGAAAAA
CAAGAGATACTTTTGCAGGAAGTGGCATTCACTCAAAGGAAAGCAGTTATTCATGAGAGA
GTCTGCAAAAGTGATGAAACTGGGGAGAAGAGTGGTCTGAATTCCAGTCTATTTTCATCC
CCAGTTATACCCATAAGAAACCATTTTCATAAACATGTATCACATGCTAAAAAAATGGCAT
CTTAATGCTGCTGTAAACAGTCATCAGAAGATTAATGAGAATGAGACCTCAAA
CA

Sequence 1568

Sequence 1569

CGCGTCCGTTTCTCCTGGCACCCTGTATTCATGGCCTTGGCGTTCTGCCTCTGCATGGCT GAAGCCATCCTACTCTTCTCACCTGAACACTCCCTGTTCTTCTTCTGCTCCCGAAAAGCA

TABLE 1 259/467

CGGATCCGGCTCCACTGGGCAGGCAGACCCTAGCCATCCTCTGTGCAGCTCTGGGCCTG GGCTTCATCATCTCCAGCAGGACCCGCAGTGAGCTGCCTCATCTGGTGTCCTGGCACAGC TGGGTGGGAGCCCTGACACTGCTGGCCACTGCTGTCCAGGCACTGTGTGGGCTCTGCCTC CTTTGTCCCCGGGCAGCCAGGGTCTCAAGGGTGGCTCCAAGCTCTACCATCTGACA TGTGGACTGGGTGTCTACCTGATGGCTACAGTAACGGTGCTTCTGGGCATGTACTCAGT ATGGTTCCAGGCCCAGATCAAAGGTGCGGCCTGGTACCTGTGCCTG Sequence 1570

Sequence 1571

Sequence 1572

CCGAACAANGTGGCCACCCAGGTTTTTAACCCAAGTCTAGTGGTCATCCTATTCTTTCCA CACCAACATGCCAAAAGCCTTACCTNGAAAGAAAATATAATTTGCAAGAAGCATCACAGT GCCGGGGTCTATATTCTCGATCAGGTTGNTAATTTTCCCATGGGTTTTTTGACTGATAAA GNCATTGATCTGCTTCTGAGCCATTTCCAAATTCTGAAAGTTGGTAAGGATGGTTTCGGN ACTGTAAAAGTTCTTGGCATCTTCC

Sequence 1573

CGCGTCCNGGNCGGAGAAGACAGTAGGGATACTGGATATGGGAGGAGCCTCTCTCCAAAT TGCTTATGAAGTTCCTACCTCAACCTCTGTCCTTCCTGCAAAGCAGGAAGAAGCTGCCAA GATCCTGCTGGCTGAGTTCAACCTGGGCTGTGATGTGCAACACACTGAACACGTGTACAG GGTTTATGTCACAACTTTTCTGGGTTTCGGAGGCAACTTTGCCCGGCAGCGCTACGAAGA CCTTGTTCTGAATGAAACTCTTAACAAAAACAGATTGCTTGGTCAGAAGACAGGTCTGAG TCCCGACAATCCATTTCTGGATCCCTGCCTGCCAGTGGGACTCACAGATGTGGT Sequence 1574

CGCCGTCCNGTTTACTTGGAGTGTCCAAAACTGCAAGCAGTAGAGAAATAAGACAAGCTT
TCAAGANNNTGGCATTGAAGTTACATCCTGATAAAAACCCGAATAACCCAAATGCACATG
GCGATTTTTTAAAAATAAATAGAGCATATGAAGTACTCAAAGATGAAGATCTACGGAAAA
AGTATGACAAATATGGAGAAAAGGGACTTGAGGATAATCAAGGTGGCCNGTATGAAAGCT
GGAACTATTATCGTTATGATTTTGGTATTTATGATGATGATCCTGAAATCATAACATTGG
AAAGAAGAAGAAATTTGATGCTGCTGTTAATTCTGGAGAACTGTGGTTTTTTAC
Sequence 1575

Sequence 1576

GACCACGCGTCCGCGCACCGCTTCATTGAGGCTGCAAGAGCACACGGGCACCCACGTGCT

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GGTCCACTGCAAGATGGGCGTCAGCCGCTCAGCGGCCACAGTGCTGGCCTATGCCATGAA GCAGTACGAATGCAGCCTGGAGCAGGCCCTGCGCCACGTGCAGGAGCTCCGGCCCATCGC CCGCCCCAACCCTGGCTTCCTGCGCCAGCTGCAGATCTACCAGGGCATCCTGACGCCAG CCGCCAGAGCCATGTCTGGGAGCAGAAAGTGGGTGGGGGTCTCCCCAGAGGAGCACCCAG CCCCTGAAGTCTCTACACCATTCCCACCTCTTCCGCCAGAACCTGAGGG Sequence 1577

CTACACTCAACTTCACCATCTCCAATCTCCAGTATTCACCAGATATGGCCAAGGGCTCAG
CTACATTCAACTCCACCGAGGGGGTCCTTCAGCACCTGCTCAGACCCTTGTTCCAGAAGA
GCAGCATGGGCCCCTTCTACTTGGGTTGCCAACTGATCTCCCTCAGGCCTGAGAAGGATG
GGGCAGCCACTGGTGGACCACCACCTGCACCTGACCCTGACCCTGAGCCCGGGC
TGGACATACAGCAGCTTTACTGGGAGCTGAGTCAGCTGACCCATGGTGTCACCCAACTGG
GCTTCTATGTCCTGGACAGGGATAGCCTCTTCATCAATGGCTATGCACCCCAGAATTTAT
CAATCCGGGGCGAGTACCAGATAAATTTCCACATTGTCAACTGGAACCTCAGTAATCCAG
ACCCCACATNCTCAGAGTACATCACCCTGCTGAGGGACATCCAGGACAACGTCACCACC
TTTTACAAAGGCAGTCAAACTACATGACACATTCCGCTTCTGCCTGGTCACCAACTTGAC
GATGGACTTCCGTGTTGGTCACTGTCAANGCATTGGTCTTCTTCAATTTG
Sequence 1578

GCGCCGCCGGCAGGTACCTAACCTACCTTTAAGACTGGGATAACTATTGNNNTNCAAT AGNTTTATACCGGATATAGTTATTTATCGCATGATGAGTAATAGAAAGGAGCTTCACAGC TTCACTTAAAAATGGGGGTGCGGAACATTAGTTAGTTGGTAGGGTAATGGCCTACCAAGA CGATGATGTTTAGCCGGGCCGAGAGGCTGTACCT

Sequence 1579

Sequence 1583

Sequence 1584

TCTTCGANCACGNTTCGGGCGGCTTTTCCCCGGGCAAGGCTTCTAAATCGGGGGGGCTTC CTTTTAGGGGGTTCCGAATTTAAGTGGCNTATAACGGGCANCCTTCGAACCCCCAAAAAA AACTTTG

Sequence 1585

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Sequence 1586

Sequence 1587

Sequence 1588

CGGGCAGGTACCTAACCTACCTTTAAGACTGGGATAACTATTGGAAACAATAGCTAATAC CGGATATAGTTATTTATCGCATGATGAGTAATAGAAAGGAGCTTCACAGCTTCACTTAAA AATGGGGGTGCGGAACATTAGTTAGTTGGTAGGGTAATGGCCTACCAAGACGATGATGTT TAGCCGGGCCGAGAGGCTGTACCT

Sequence 1589

Sequence 1590

GGCGAATTGGAGCTCCCCGCGGTGGCGGCCGAGGTACTGTGATATCCACATATTTTTGAG
AAAAATTCCCAAGCCAGGCGAATGTGGATTGGAATAAAGACATAGGCAGTGTATACCACC
ATAGCAATAATGGTTAGTAAGATGGTGTTAAACATAGATCGCTCCCAGGGCTCTAAAACA
GCACAGCAGCTAATGATTTGGTATTGATAGTAGAGCCAGGAGAAATATTCCTTCACACGC
CTCAAATCCATGGTTGGCTCCTTCAAGCTGCAGTAAGTTTGTCCTAAGAAAGTCCAGGTC
TGGTTCTTCAGCCTTGCTCCTTC

Sequence 1591

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CCACCGTAAGATTCATATAATCTAATCAAAGATCTACCAACTGGTTGTTTTACCCTGGAT CCAGATTCACCAATTAAACCTAAAATTTTTCCTTGTTGGATCTAAAATTTTACCGTTATC AACAGCTTTGACAACCCAAANTTATTGGAAAAATATTTTTTTAAGCTTTGAACTTTTAAG GGTGGGTTAACTTGCATTA

Sequence 1592

Sequence 1594

Sequence 1593

CCGCGGTGGCGCCCCGGGCAGGTAGGCTGTCTACACTGACATCATCCAGGGCAAGCT GGACCAGCGAAACCAGCTGCTGGAAGTGGATTTCTGCATTGGCCGTGACATCCGAAAGAA GGATATCAATAATATTGTCAAGACCCTGCATGAATGGTGTGATGGCTGTGAAGCAGTTCT ACTGGGCATNGAGCAGCAAGTTCTGAGAGCCAACCAGTACCTT Sequence 1595

ACTINITITITITITITITITAAGCGCCCGGCATTITCTAAAAAAATCATTT
TATTTGGNAAAAGGGTTTTAACAGNTATACCTTTCTAGCTAAAAGAAAAAGAAATAGCGGG
ATGTACCT

Sequence 1597

AGGTACGAAGAGAAAGGAATCAAAGCCTACTANCTCAAAAAATTGTCAAATTGCAAATGA GGACATCTAGAGAGGAAGAAAGGAAAAAAGGAACTAAAAAACAGAAACAATTAACAGTAA GTTCTTAACTATCAATAATTATTTTAAAAGTAAATAGATTAAATTATCTAATCAAAAGAC ATTGAATGGCTGAATGGATTAAAAAACAAGATCAACTATACATTGCCCATCAGAGATTCA TTTTAGCTTTAAGGATAAACACTGGTTGAAAGTGAAAAAAGTCAAGGCTGGGCATGGTGG CTCATGTCTATAATTCCAGCACTTTGGGAGGCCAAGGTGGGCAGATAATCTGAGGTCAGG AGTTTGA

Sequence 1598

CCGGGCAGGTACCACCTGAAGACCCTCACACTCAACTTCACCATCTCCAATCTCCAGTAT
TCACCAGATATGGGCAAGGGCTCAGCTACATTCAACTCCACCGAGGGGGTCCTTCAGCAC
CTGCTCAGACCCTTGTTCCAGAAGAGCAGCATGGGCCCCTTCTACTTGGGTTGCCAACTG
ATCTCCCTCAGGCCTGAGAAGGATGGGGCAGCCACTGGTGTGGACACCACCGGCACCTAC
CACCCTGACCCTGTGGGCCCCGGGCTGGACATACAGCAGCTTTACTGGGAGCTGAGTCAG
CTGACCCATGGTGTCACCCAACTGGGCTTCTATGTCCTGGACAGGGATAGCCTCTTCATC
AATGGCTATGCACCCAGAATTTAT

Sequence 1599

CTTAGGGCGAATTGGAGCTCCCGCGGTGGCGGCCCGAGGTACACAGGACCAATGCTGCC

TABLE 1 263/467

CATCCACATGGAATTTACAAACATTCTACAGCGCAAAAGGCTCCAGACTTTGATGTCAGT
GGATGATTCTGTGGAGAGGCTGTATAACATGCTCGTGGAGACGGGGGAGCTGGAGAATAC
TTACATCATTTACACCGCCGACCATGGTTACCATATTGGGCAGTTTGGACTGGTCAAGGG
GAAATCCATGCCATATGACTTTGATATTCGTGTGCCTTTTTTTATTCGTGGTCCAAGTGT
AGAACCAGGATCAATAGTCCCACAGATCGTTCTCAACATTGACTTGGCCCCCACGATCCT
GGATATTGCTGGGCTCGACACACCTCCTGATGTGGACGGCAAGTCTGTCCTCAAACTTCT
GGACCCAGAAAAGCCAG

Sequence 1600

TCNCCGCGGTGCCGCCCGGGCAGGTACGTTCACTGTCTCATATAATCNCAGCCTCC
TGTGTGATAGCTGGTGTCATCTCCACTTACAGATGAGGAAACTGAGGATAAGCAGGGTTG
AATAACTTGCTCGAGATCACAGAGCCACGGGTGGNGAAACAGGATACAAACCTGGTTCTG
TTTGACTCTAAGACCATTCATNTTTCCTCTGAAACTCAGTATTGCACAGTGTAGAAATGC
AGTTTTTAAGACCTCCCAAAGTGACGTGCTGNGTCACTGCCCATCATTAGCTANATTGAG
TAAATTGCTGCTTAGCCCCANTTGTTTTGACAGAATCAATAGCCCTTGCTGAGGGGCCAN
CAGCCTACGGACACAGGAGCATGCTTCATGGGCAAGACCACCATGCACACTCAGAGGGGA
AGCCACAAGGCAACCTCCACGCCACTTAAGATTTGTAGGGCTCTGAACACATCACCAGAT
ACAGACCACCTACTTATTTTTTTNCACTGTAATANCAAAGGCAGGAATCTTTTTNCTGTAG
GGTAAAGTTTGGGGG

Sequence 1601

GGCAGGTACAAGGCCCCAAAGAGGAGGAATTCCTTGTAGAGGAGCTTGTAGATGCTTCCC CTCCAGCGGAGAAGCAGGCCAGAGAAACCTCCGAAGCGGGCCTCCGCCACTTTGAGAGTG TATGAAACCGTCATGGTGCTGGGAGCCTGGGGCAGGAGGTCACAAGAGTTGCCCCCAGGG CTGTCGTTTAGTTCTCCAGACAACCTCCCTTCCACTCTGGTCTCCACACCCCAGCCTTCA CCCTGCGTCAAGTGGACAAG

Sequence 1602

AGGTACCAGTGGGGACTTCTGAAAGAACNNTACTNGTGTCAGTGGAAAAGCTGGCATTTT
GGGAAATGCTGGTCTCTCAGTCCAGGAGTCAAGGAATATGTTGACTCTCTTAATTT
TTGTAGTCTCAGAGGAAACAGACATTGATGTGGAAACAGTTGTATGCCCCATGGTGGAGG
TGGTATCCATNGGAGCTGTGGCCTTGGTTTTTTCTGAGTCAGCTAGGACAGAGGATTGTG
ACCCATGTCCAGAACTGGTGGTTTCCACATTAGTCGCTGCTGTGTTGTGGAAGGATGCA
TGGCTTCTATAGCTGTGGTGTCTTCATCTGTTGTCAGTATCTCATGTGAGGNACCTGCCC

Sequence 1603

CCGGGCAGGTACTGTGATATCCACATATTTTTGAGAAAAATTCCCAAGCCAGGCGAATGT
GGATTGGAATAAAGACATAGGCAGTGTATACCACCATAGCAATAATGGTTAGTAAGATGG
TGTTAAACATAGATCGCTCCCAGGGCTCTAAAACAGCACAGCAGCTAATGATTTGGTATT
GATAGTAGAGCCAGGAGAAATATTCCTTCACACGCCTCAAATCCATGGTTGGCTCCTTCA
GGCTGCAGTAAGTTTGTCTTAAGAAAGTCCAGGTCTGGTTCTTCAGCCTTGCTCCTCCC
GAAATGATCCTGTGTGGGTTAGTTCTCCTCTCTGGGTTGCTGTTTCCTCA
Sequence 1604

AGGGCGAATTGGAGCTCNCCGCGGTGGCGGCCGAGGTACCACCTGAAGGCCCTCACACTC
AACTTCACCATCTCCAATCTCCAGTATTCACCAGATATGGGCAAGGGCTCAGCTACATTC
AACTCCACCGAGGGGGTCCTTCAGCACCTGCTCAGACCCTTGTTCCAGAAGAGCAGCATG
GGCCCTTCTACTTGGGTTGCCAACTGATCTCCCTCAGGCCTGAGAAGGATGGGGCAGCC
ACTGGTGTGGACACCACCTGCACCTACCACCCTGACCCTGTGGGCCCCGGGCTGGACATA
CAGCAGCTTTACTGGGAGCTGAGTCAGCTGACCCATGGGTGTCACCCAACTGGGCTTCTA
TTGTCCTGGACAGGGATAGCCTCTTCATCAATGGCTATGCACCCCAAAATTTATCAATCC
GGGGGCGAGGTACCTGCCCCGGGCGGCCGCTTAAAACTAGGNGGGATCCCCCNGGCTTG
CAGGAATTTCGATATTCAAGCTTATCGATACCCGTCCNACCTTCGAGGGGGGG

CCGGGCAGGTACCACNTGAAGACCCTCACACTCAACTTCACCATCTCCAATCTCCAGTAT

TABLE 1 264/467

TCACCAGATATGGGCAAGGGCTCAGCTACATTCAACTCCACCGAGGGGGTCCTTCAGCAC
CTGCTCAGACCCTTGTTCCAGAAGAGCAGCATGGGCCCCTTCTACTTGGGTTGCCAACTG
ATCTCCCTCAGGCCTGAGAAGGATGGGGCAGCCACTGGTGTGGACACCACCTGCACCTAC
CACCCTGACCCTGTGGGCCCCGGGCTGGACATACAACAGCTTTACTGGGAGCTGAGTCAG
CTGACCCATGGTGTCACCCAACTGGGCTTCTATGTCCTGGACAGGGATAGCCTCTTCATC
AATGGCTATGCACCCCAGAATTTATCAATCCGGGGCGAGTACCT
Sequence 1606

CGGCCGCCGGGCAGGAACNNNTTTTTTGGGGGGGGGAAAACCNAGACGGAGCCNCGCN CAANGGCCCAGGCGGGGGTGNAAGGGCACCAGGGGGGGGCNCACCACAAANACCGCCGCCC GGGNGAAAGCCACNCNCCGGCCNNAGCCNCCGGAGNAACGGGGGGAACAGGGGCAGCCA TNTTTTTTTTTTGNGGGGGGNGNANGGGGNGGANNCNCCAGGNAAAAANCANGCNGGCCA GGGGGGGGGAACNCCNGACCTNATGANGCACCCGCCNNGGNCNCCCAAAANGCGGGGA NNANAGGGGNGAGCCACCGNGCCNAGCNGACGG

Sequence 1607

CGAGTTACCAGAAGGAGAGATCACCACCATCGAGATCCACCGCACTAACCCGTACATCCA GTTAGGAATCAGCATCGTTGGCGGCAATGAGACGCCACTGATCAACATCGTNATTCAGGA AGTNTACCGGGATGGGGCCATCGCCAGAGATGGAAGGCTCCTTGCCGGAGACCAGATTCT TNAGGTCAACAACTGTGATATCATGCAACGTGTCCCATAACTACGCCCGGGCTGNCCTTT CCCAGCCCTGCAGNACCCTGCACCTGACAGNGCTTCGGGAGCGGCNGCTTNGGCAGTCGT GCAAA

Sequence 1608

CGAGCCTTTAGATGGCGTCTCCTCAGGGGGGCCAGATTGCGATCGCGATGAGGCTTNGGA ACCAGCTCCAGTCAGTGTACAAGATGGACCCGCTACGGAACGAGGAGGAGGTTCGAGTGA AGATCAAAGACTTGAATGAACACATTTGTTTGCTGCCTATGCGCCGGCTACTTNGNGGAT GCCACCACCATCACAGAGTGTCTTCATACTTTCTGCAAGAGTTGTATTGTGAAGTACCTN CAAACTAGCAAGTACTGCCCCATGTGCAACATTAAGATCCACGAGACACAGCCACTGCTC AACCTNAAACTGGACCGGGTCATGCNGGACATCGTGTATAAGCTGGTGCCTGGCTT Sequence 1609

Sequence 1610

CGCGTCCGGCGGCGCGGCTGAGGAGGGCCCGGCCTGCGAGAGCCTCAGTGGGAGCCGGC
TCAGCCCTCGGCCACCATGTCGGCGCCGCTCGGAGGAGGAGGAGTACTGCGCGGCTGGTGA
TGGAGGCGCAGCCGGAGTGGCTGCGCGCCCNAGGTGAAGCGGNTGTCCCACGAGCTGGCCG
AGACCACNCGTGAGAAGATCCAGGCGCCGAGTACGGGCTGGCGGTGCTCGAGGAGAAGC
ACCAGCTCAAGCTGCAGTTCGAGGAGCTCGAGGTGGACTATCAGGCTATCCGCAGCGAGA
TGGAGCANCTCAAGGAGGCCTTTGGACAAGCACACACACACAAAACCACAAGAAGGTGG

CGCGTTCGAGTCTGGAGACGACGTTNCGAAATGGCACCTCGCAAAGGGGAACGGAAAAGA AGGAATGAACAGGTCATCAGCCTTGGACCTCAGGTGGCTGAAGGAGAGAATGTATTTGGN GTCTGCCACATCTTTGCATTCTTCAATGATACCTTTGTCCATGTTANTGAACTTTCTGGC NAGTGAGTACTTCAGAAAGGCATNAAACANGCCTCAAAGGGAC

Sequence 1612

CCCGCGTCCGCCCACGCGTCCGGGCTCGGCTGCACCGGGGGGATCGCGCCTGGCAGACC

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Sequence 1613

Sequence 1614

Sequence 1615

Sequence 1616

GGNCGAGCGCCCTTGCGGGGGGGGGTATCCCGGCGCCCTAAGACCCCACGACCNCNNGCA CCGGCCGNTGCTGCNAGACCCCGGCCCGNGTCGGTCCGATGTCGCCCCCGGNCCCGGCG GAAACGCCTCCCTNCTGGCCAGGCTGTTCNAGCACCCGCTT

Sequence 1617

Sequence 1618

Sequence 1619

TABLE 1 266/467

Sequence 1621

GTCGCCCGCGTCCGGGGCCCGCGGGCCTCGCCTCCGCCACCTCGAGCTGCGG
TAGCAGCGACTCATGAGAGCGCGGCCGGAGGACAGATTTGATAATGGGCTGCATTAAAAG
TAAAGAAAACAAAAGTCCAGCCATTAAATACAGACCTGAAAATACTCCAGAGCCTGTCAG
TACAAGTGTGAGCCATTATGGAGCAGAACCCACTACAGTGTCACCATGTCCGTCATCTTC
AGCAAAGGGAACAGCAGTTAATTTCAGCAGTCTTTCCATGACACCATTTGGAGGATCCTC
AGGGGTAACGCCTTTTGGGAGGTGCATCTTCCTCATTTTCAGTGGTGCCAAGTTCATATC
CTGCTGGTTTAACAGGGNGGNGGTACTATATTTTGNGGCCTTATATGATTATGAAGCTAG
AACTCCAGAAAGACCTTTCATTTAAGAAGGGTGAAAGATTTCAAATAATTAACAATACNG
AAGGAGATTGGTGG

Sequence 1622

Sequence 1623

GGAGTCGACCNCGCGTCCGAGCCGGGCCGGGCCGATGTGGAGCGCGGGCCGCGGGGGC TGCCTGGCCGGTGCTGTTGGGGCTGCTGCTGCGCGCTGTTAGTGCCGGGCGGTGGTGCCGC CAAGACCGGTGCGGAGCTCGTGACCTGCGGGTCGGTGCTGAAGCTGCTCAATACGCACCA CCGCGTGCGGCTGCACTCGCACGACATCAAATACGGATCCGGCAGCAGCAGCAATCGGT GACCGGCGTAGAGGCCGTCGGACGCCAATAGCTACTGGCGGATCCGCGGCGGCTCGG AGGGCCGGGTGCCCGCGCGGGTCC

Sequence 1624

CGCGTCCGGGGCAGCCGCCGCGGAGTTTTCCGCCCGGCGCTGACGGCTGCTGCGCCC GCGGCTCCCCAGTGCCCCGAGTGCCCCGCGGGCCCGCGAGCGGGAGTGGGACCCAGCCC CTAGGCAGAACCCAGGCGCCGGCCCGGGACGCCCGCGAGAGAGCCACTCCCGCCCACG TCCCATTTCGCCCCTCGCGTCCGGAGTCCCCGTGGCCAGATCTAACCATGAGCTACCCTG GCTATCCCCCGCCCCAGGTGGCTACCCACCAGCTGCACCAGGTGGTGCCCTGGGGG AGGTGCTGCCTACCCTCCTCCGCCAGCATGCCCCCCATCGGGCTGGATTAACGTGGCCA CCTATGCGGGGGCAAGTTCAACCAGGGACTATCTTCTCGGGAATGGCGGCCAACATTGTC TGGGGACATTTGGAGGGAGCCAACATGCCCAAACCTGGACCCTGGGGCCCCTGGGGGCTG

TABLE 1 267/467

Sequence 1625

Sequence 1628

CCTAAGGGCAACAAGGGCGTCCTGGCCAGCCGGGCTTTGAGGGAGAGCAGGGGACCAGA GGTGCACAGGGCCCAGCTGGTCCTGCTGGTCCTCCAGGGCTGATAGGAGAACAAGGCATT TCTGGACCTCGGGGAAGCGGAGGTGCCGCTGGTGCTCCTGGAGAACGAGGCAGAACCCGG TCCACTGGGAAGAAAGGGTGAGCCCGGAGAGCCAAAAGGAGGAATCGGCAACCG GGGCCCTCGTGGGGAGACGGGAGATGACGGGAGAGACCAAAAGGAGTAACCCAGGTN AACCTGGGCTAAATGGAACAACAGGGACCCAAAGGCATTNAGAGGCCCGAAGGGGA Sequence 1629

AGTCGCCCGCGTCCGCTGTGCCTGAAGGAGACTGGTTTTGTCCAGAATGTCGACCAAAG CAACGTTCTAGAAGACTCTCCTCTAGACAGAGACCATCCTTGGAAAGTGATGAAGATGTG GAAGACAGTATGGGAGGTGAGGATGAAGATTGATGGCGATGAAGAAGAAGATCAAAGT GAGGAGGAAGAGTATGAGGTAGAACAAGATGAAGATGACTCTCAAGAAGAGGAAGAAGTC AGCCTACCCAAACGAGGAAGACCACAAGTTAGATTGCCAGTTAAAACAAGAGGGAAACTT AGCTCTTCTTTCTCAAGTCGTGGCCAACAACAAGGAACCTGGAAGATACCCTTCAAGGAG TCAGCAGAGCACACCCAAAACAACTGTTTTCTTCTAAAACTGGGTAGAAGCCTAAGAAAG ATAAACTCTGCTCCTCCTACAGAAACAAATCTT

Sequence 1630

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AGCCCAGAGCAACAAGCTTTCAGCAACACAAGAAATTCAGGAAGCTGCTTTCAAAAAAGAACCTAA

Sequence 1631

Sequence 1632

CGTCCGTTTGTTTAATATTTTTTTTCTCTCTTGAACAAAACTGAGATAATTTAGAAAACA GGTGCTTAATTGCAATAAAATTACTATGAAGATATTTAAAAATCACGACATTGTAAAATC TCACTTTAGATCATCAAAGAAAACCATTGTTACTATCTCCTTTGAGCTTAGGAAAATGTA CAAGAGAACAAATTAAAATTGAAAAAATTGATTTCACTTAGAAAAACTTCTAGGAACAGGG TGAACCACTGATTTTAATTTGCCTAATTATCTTATGACAAGTATCAAATTAAGATGACAC TTAAAGGATCCTTAGCATTTAACTTAATGATGAGAAAAAGTGCTCAATAGGACAGTTCC CCAGTTAAGGGGTAATGGAGATGCCCATTTTCAGGAGGACCATTCTAAGAAGATATTTTT GGATTCATTAAAAAACATTTAAATAAAAAGCCCTTCTTCAAGATTGGGAAC

Sequence 1633

Sequence 1634

CCCCGCGTCCCGGTTGGCCGGGCGAGGTCTTCGCTGAGGCCCGGGGCGGGGTGGCGCA CCCCTGATTGCGGTGCCACGGACTGCTCCTGCTGGGCGGAGAGGACAGATTTTGCAAAGC GGAGGCTTGCGACGGGTCCTGCAGGGGGACAGTGAGGAAAGGGCCCGCCTCGTNTCCGCT CCTGGGGGACCCGCAGAAATAAGAATCAAACTCCACAATGACAACCTATTTGGAATTCAT TCAACAAAAATGAAGAACGAGAATGGGAGTCCCGATTTAGT

Sequence 1635

Sequence 1636

CCNCGCGTCCGCGACGCGTGGGCGGACGCGTGGGCTTCTGCAGCAAGCTCAGGAGAGCT GCTGTCTTCCCTCCCGCCCACCAGCAACGCACCCTCTGACCCTGCCACAACTACTGCAAA GGCAGACGCTGCCTCCTCACTCACTGTGGATGTGACGCCCCCCACTGCCAAGGCCCCCAC CACCGTTGAGGACAGAGTCGGCGACTCCACCCCAGTCAGCGAGAAGCCTGTTTCTGCGGC TGTGGATGCCAATGCTTCTGAGTCACCTTAACTTTGAACCATTCTTTGGAATTGCGTGG TATATTTAACCACGGGAGGCGTGTCTGGAAACGCAAACTATCATTAATTTCATACTAGGT TTGTACCGTATCTGTAGGCATTCCTGTAAATAATTCCAAGGGGGAAAACTAAACNGGGAC

TABLE 1 269/467

GTGGGGTTGTATCCTGCCAGGTTTGAGTGGGGGGCTCACACCTAGGGTGAGAAGTCAGAAA GCGCTTGTATTTTAAACAACCAAAAAGAATTGAAAGGGTG

Sequence 1637

CGCGTCCGGCTCCCGCACCCCTCGCACTCNCTCTGGCCGGNCCAGGGCGGCCTTCAGC CCAACCTTGCCCAGCCCCACGGGCGCCACGGAACCCGCTNGATCTCGCCGCCAACTGGTA GACA

Sequence 1640

GTCGCCACGCGTCCGGCCGGGCCGGGCCGGGCAGCCGGGAAGCGGGTGGGGTGTGTTA CCCAGTAGCTNCTGGGACATCGNTCGGGTACGCTCCACGCCGTCNCAGCCACTGCTGTGG TCGCCGGTC

Sequence 1641

Sequence 1642

TABLE 1 270/467

CAGGCCAGGCAAGGGGCTGGTCCATGATGTCATCAGGCACCCAGGTTCCTACTGGCTTTGCATGTGGCCACAGGTTAGCAACAAANGGAGGCTGTAAATTT

Sequence 1644

Sequence 1645

Sequence 1646

Sequence 1647

GGTGTCGCCCCGCGTTCGGTTTCTCCTAATTTATATTTCCGATACATANGTGTAGAACA
GGAATTTGCAGAAGCCATTTAAGTTATCTTTTGAGGTAANGCTCTGATTTAGCATTTATT
CTGATAAAATCTAATACATCATGGGATATATATAAAGCAACTTAATTCTTGTGGTGTAGT
CTTAATAGTTTTGAATGTTGACTGAATGTCTATAAAATTGTGAGTTTGTCTTTGTTACAT
TCCAGTGTTTCTGCCTCTTGGCATGCTTAAAGCACGGCTTACTTCATCTGCTCCTTACAC
ACTAAAATGCTGTTAGTGTGCTCAACTACAGAAATAGCCGCTGCTAAGTTGATGTAGATT
TTCTACTTGAATATTTTTATGGTTGTAGGAACCTCAGGAGGGTCAGTGTTTACTGGTTTA
TATATGCCTTCTTTTTCCTGTTTGAGCTTCTCTTTTGAAGGGATTCTAACAGAACAAAA
GCTGCTGATCACCCTAAGTTGGAAACAGNAAAGGNGTAATTAATATAACTTAATGC
Sequence 1648

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ACTGCGGTATTCCAGTTCTTCTGACACCGGATGGGTGCTTGGGAACCGTTTGAGCCTTAT AGATCATTTACATTCAATTT

Sequence 1649

Sequence 1650

Sequence 1651

Sequence 1652

Sequence 1653

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Sequence 1654

CGCGTCGCTGACATTTCCTAGGAAGCTNGGAAAAGGAAAGTGAAGGAATGGTCTAAAGA
AATGACCATTCACACTGATTTTGTCTGGACAGTCTGGCCGCAGGTTATTCATAGATTATT
CAGCCTTTGCAGGACTTGGATTCAGGGTTTTACTCAGTCCCTTTACCTTAGGTGGAATCT
TCTTAAATTGAAATTTTTGGTAAGGAATTCATTTCACAGGTAGTGTTTCAGACTCTGAAA
GCCCTGACTTGGTTCTTGGCTTCTACTGTACTAGTTACTAGTTACTGGTACTGTTGCCAA
GCAATCTGCTTGGAATTTGTGGATCCCTGCTGTTCCCTAATCCCACCCCCTGCCCTGAGA
CAGTGAATGTAGTCCGTGAAGGGAGTGCCTCTCTGGGACCCCCTGTGTTGTTACAGGCTG
TGCAGTGCAACAATTCCAGCAAAAATACCCTATCCCCGCACTTAGTCATTCGTGGTAACT
AACAATTTTGAAATACTCATATAAAATGAACAGGAAAGTGGTTAGTG
Sequence 1655

Sequence 1656

CNCTAACCCCGAACTCTAGATCGTCTTGCTTGTTTGTCTGAAGAAGAGGGAATGAAATAGAA AGTGGAAAAATATTTTCAGAGCATCTTCCCTTAAGTAAGCTACAGCAAGGCATAAAA TCTGGTACATACCTTCAAGGAACATTTAGAGCTAGCAGGGAAAATTACTTGGAAGCTACA GTATGGATTCATGGCGACAGTGAAGAAAATAAAGAGATAATCTTACAGGGACTTAAACAT TTAAACAGAGCTGTTCACGAAGATATTGTGGCTGTGGAGCTTCTCCCCAAGAGTCAGTGG GTAGCACCATCTTCTGTGGTTTTACATGATGAAGGTCAAAATGAAGAAGATGTGGAGAAA GAAGAAGAAGAACGAATGCTTAAGACTGCTGTAAGCGAGAAAATGTTGAAGCCTACA GGTAGGAGTTGTAGGAATAATAAAAAGGAATTGGA

Sequence 1657

Sequence 1658

Sequence 1659

CGACCNCGCGTCCGGCTGNTGACCCCATGCTGAGTGGCCNGTGGGGAGCGCGCCCGGCA

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Sequence 1660

Sequence 1661

Sequence 1662

GACCACGCGTCCGGAAGGAAGGGACGGGCTGAGTTCCCCGACGAGAGACACACCCAGATT TTCCTGCAGCTTGGGAGAGAGACGCCAGATCCCTGCAGGAGCCTTGGGCCTGCCGGAGTCCCTTAGCCAGGATGGAGGCTGTTGTGAACTTGTACCAAGAGGTGATGAAGCACGCAGATCCCCGGATCCAGGGCTACCCTCTGATGGGGTCCCCCTTGCTAATGACCTCCATTCTNCTGACCTACGTGTACTTCGTTCTCTCACTTGGGCCTCGNATCATGGCTAATCGGAAGCCCTT Sequence 1663

CCGCGTCCGGGGGTTGGTACCCGAGCGCCTTCCCCTCACCTCACCAGAGAAGAGCATCC
GGTTGCTTTTTAAAGCTTTTAGCCTGCCCTAGCAAGGACAAAGCATGTTAGATTAGAGAT
GCTTCTGCTGATCGCAGGGGTTCTTATTTGAAAACATCTATGATGGGGGTGGGGTGGGAG
GAGACAGGTTGTGGTTATGCAGGAAAATCTTGTCCTAAAAATATATGAGTTTGGGGGTAA
GGGGTGGGATAGCCAAGCAAAATCAGTAATTATTTTAAAATGAACATATGTATTTTTATT
AACTTTTAGTTAAATACAGATTTTACAACGAGGTCAGCATAAACCTAAATCTATATAGAG
GGCTAACTCAGGCATTGTCTTGTTTATTTGTAGACTGGATTAAAAACAACCTGTCCTGTT
TTGTNAGTTCCCAGCTTCTTTCGTTTAGAATAAATTAGACCAAAAGAA
Sequence 1665

TABLE 1 274/467

GCGTNCGCTTAATGTCAATGTGGCCTGGGCTGGAGGTCTGGACCCCCCATGGGGGATCC
TGAGTACCTGGCTGCTTTCAGGATAGTCGTGATGCCCATCGCCCGAGAGTTCTCTCCAGA
CCTAGTCCTGGTGTCTGCTGGATTTGATGCTGCTGAGGGTCACCCGGCCCCACTGGGTGG
CTACCATGTTTCTGCCAAATGTTTTGGATACATGACGCAGCAACTGATGAACCTGGCAGG
AGGCGCAGTGGTGCTGGCCTTGGAGGGTGGCCATGACCTCACAGCCATCTGTGACGCCTC
TGAGGCCTGTGTGGCTGCTCTTCTGGGTAACAGGGTGGATCCCCTTTCAGAAGAAGACTG
GAAACAGAAACCCAACCTCAATGCCATCCGCTCTCTGGAGGCCGTGATCCGGGTGCACAG
TAAGTGTGGAGATGGGACACTCGCTGAGCTCAGACTGAAGGATCTTGGT
Sequence 1666

Sequence 1667

NCGCGTCCGACACTATTTAGAGAGCTCCCTTCCCACCTCTCTGCCCAGCCTTGTTACCTC
ACTTCTGCTCTGGCCATGGCTGTGAAGGGCCCAGCCAGCTCCCTGTTTTGATGTTCTGTG
CAACAGCTCCGGGGTCTTGTGACTGGAGATCCTCAACAGGCCCTGGAGCCAGGACTGGAG
TCTTGGCAGCTGATGAGCACCCTTGCCGGCCAGGAGGAGCTGATGCTGACGATCTCCC
CAACATCTGAAGGCTTAAAGAACATTGTCGTTCTTCAGCCCTCCTTGCTTCTCTCAATAC
AATAAGACATTGCAGAAGCAAAAGGGTGGCCTCTGCTCCAGGCAAGGCAGCTGGCTCTGT
CTGGGGGCGTCGGCCTGGGCTTGGGTGCCACGTGCTGAGATTGCATAGTCAAAACAAGC
CATTTTTGCCAACAATAGCTTGTGGCTCCCACATTTTTCTACCCTTGCACTNAANGGCCA
GACCACTCTNTGCATGGACCAANACCATNTTTCCAAACCCATGGGGCTTTTTTTNCC
Sequence 1668

Sequence 1670

CGACCNCGCGTCCGGTCTGAAGGGTCTGGCTGGTGAGCCAGGTTTTAAAGGCAGCCGAGG GGACCCTGGGCCCCCAGGACCACCTCCTGTCATCCTGCCAGGAATGAAAGACATTAAAGG AGAAAAGGAGATGAAGGGCCTATGGGGCTGAAAGGATACCTGGGCGCAAAAGGTATCCA AGGAATGCCAGGCATCCCAGGGCTGTCAGGAATCCCTGGGCTGCCTGGGAGGCCCGGCCA



CATCAAAGGAGTCAAGGGAGACATCGGAGTCCCCGGCATCCCCGGTTTGCCAGGATTCCC TGGGGTGGCCCCCCTGGAATTACGGGATTCCCAGGATTCATAGGAAGCCGGGGTGA CAAAGGTGCCCCAGGGAGAGCAGGCCTGTATGGCGAGATTGGCNCGACTGGTGATTTCGG TGACATCGGGGACACTATAAATTTACCAGGAAGACCAGGCCTGAAGGGGGAGCGGNGCAC CACTGGAATACCAGGTCTGAAGGGATTCTTTGGAGAGAAG

Sequence 1671

Sequence 1672

Sequence 1673

GTCGACCACGCGTCCGGCCAGAGCTGAGTGGCAGCCGCCTCCCTTATGCAGGACATGTGC
TCTCGGCTTCACCAGGGTTCTGACCGGGTCTGCTTCTGCATTCACAGCGCCTCCTGGACC
TGAAGGCATCTGAGTGTGAGACCCTGTTCTAACTCTTAGAAGTGACATTGTAAGAGGTGG
TGGGGACCAGCTAATTGGTCCAACCCAGCCTGAGTGCACCACCCTTTGAACAAATGTATC
AGTGATGAAAATTTGCCTTTGCCCCGGCTTGCCTGTAATCCCAGCACTTTGGGAGGCCGA
GGTGGGCGGATCACTTGAGGTCGGGAGTTCAGGACCAGCCTGGCCAGCGTGGCGAAACCC
CGTCTCTACTAAACATAAAAAAATTAGTCAGGTGTGGCGGTGCCTGTGCCTGGTCCCAGC
TATTCAGGAGGCTGAGGCACCAGAATTGCTTGA

Sequence 1674

Sequence 1675

TABLE 1 276/467

GGGACATGGGCGGCTTTGCCATTCTGGTGCAAGAAGGCCA

Sequence 1676

TCCCTCTGCTGATGATGGATGCCCCTAACACCTGTGCCTAACACCCCTACTGAACCCCAC
AGCTCCAGCCTTAGTTTTTGGAGTCAAGTGTTAAAGGTTTCTGGCCAGAGGAATTGGGGT
CTTGCCATCCCTGCAATAGCCCTTTTATGGGCTCTGGGAGACAGCTTTAGGGAATAAATG
GGGATTTTCCCCTTTTTCTACCCACTCCTTTGCTTCCTCCAAGACTTACCCAACTCCTTC
CCCCTCAGAGAACCAAATAGCCTGAGGAAGCAGGAGAGTTCCTGGTTATGGCAGATTCTT
GGTGATTTGGGGCTTCAAGACAGTAGGTGAGAGAGTGCTGTCAGGGACGTATCTTCAT
ACCAAAGTCACTGGTCCTTTCTCAGCCTCTCTCGTGCTTTTCTCCTAATGACCATATTTT
TGCCAAAAATTGGGAATATGTTATCTGACAGACCAGAATATTTGAAGGTTTGGGCTG
Sequence 1677

GCGCCGCGATATNCGGATCAACCTATGGTNTCAATATTGTNAGTTATTCAGCATAAACA GAATTATTTCCCAANACTTGATCTGAAATATTNNTAATGGTCNTACTNGAAACTTATATT CTTNCTGGGAGNGANGTNTTTATCATTTTTCCATGGAGACAGGTTCTAACTCTGTTGCCC AGGCTGCANTGCAGTGATCTGATCATAGCTCACTGCAGCCTGAAACTCCTGGGTGTCAAG TGATCTCTGGCCTCAGCCTCCCAAGTAGTTGGAACTTCAGATACGTGCCACCACAACCAG CTAATTTATTTTTTAGAGATGAGGTNTCGCTATGTNGCCCAGTCTGGCCNNCTAGCCNCA AGTGATCTGGCCATCTNAGCCTTCAGTTGGAGATGTCTGATTTATGTTAATATAAGAAAG CTGTTGATCGTTTATCATAAANGCATTT

Sequence 1678

Sequence 1679

Sequence 1680

Sequence 1681

CCGGCAAAGCAGGACTCCTGATTTATATGTCCCTCCTCGGCAATCCTCTCACCCCAC CTCCCCTGAGAACCTCAGTTCTTCCTAAATTGCTAAAGCTGAGGGGAAAGGGATGCTTTG



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CGGCAAAGGCGCTGCTCCAAGCTTGCTTTACATGCCTCTCAGTTCCTCTCGCACTA CAGAGTGGTAGCGAACAAAAGCGTTCGCCCTAGAAGCGACCTGAATGGAAAAATCTGCAC ACGAACTAATGGGTTTGCACGGAAAGTAGGGAACCGGGTCTGCAGCATTCCCTGGAGAC AGACTTTCTGGTTTGCAAGGGTCCAAGGCAGCCATCAGCCCGGCTGTGCCCTCCCA CCCTGCCTCCCACCCAGTTGATTCTCTCTTTGTGTAAGTTTAGCCCCTCTGAGGGTGGTG GAGTGAGACACCCATCAGATATATATACGATTCATCAGTCGGCACTTAAAAAAG Sequence 1682

TCACCNCGCGTCCGAAAAACGCAGATGATATACCTGCAACATCNGTCATGGCTGCGCCCT GTGCTCAGAAGCAACCCGGGTGGAATATTGCTGGTGCAACAGTGGCAGGGCACAGTGCCA CTCAGTGCCTGTCAAAAGTTGCAGCGAGCCAAGGTGTTTCAACGGGGGCACCTGCCAGCA GGCCCTGTACTTCTCAGATTTCGTGTGCCAGTGCCCCGAAGGATTTGCTGGGAAGTGCTG TGAAATAGATACCAGGGCCACGTGCTACGAGGACCAGGGCATCAGCTACAGGGGCACGTG GAGCACAGCGGAGAGTGGCCCAGACGCCACTGGAACAGCAGCCGCGTTGGCCCAG AAGCCCTACAGCGGGCGGAGGCCAGACGCCATCAGGCTGGGCCTGGGGAACCACAACTAC TGCAGAAACCCAAGATCGAGACTCAAAGCCCTGGTGCTACGTCTTTAAGGCGGGG Sequence 1683

Sequence 1684

Sequence 1685

Sequence 1686

TABLE 1 278/467

AAACATAAAAGAATGTATCCTTAGTACTGGTTCTTAAACAGCCCATAAAAACCCATTGGC CTGAAGCTTATATCTCAGGCCTATGCCCATCTTATAGTCTTGGAAGACAAAA Sequence 1687

Sequence 1689

Sequence 1690

Sequence 1691

Sequence 1692

ACAGAATTTAGGGGTGGAAAGCACTTGNGCTTTAGCTNTTTCATATTAAATATAT CTATATTTAAACATTCATGGCATAGATGATGATTTACAGACAATTTAAAAGTTCAAGTCT GTACTGTTACAGTTTGAGAATTTGTAGTATTACATCATTACATAAGTCATTTAGTAACA

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Sequence 1693

CGGTTAACATGGCCGTCACCGACAGCCTCAGCCGGGCTGCGACTGTCTTGGCAACTGTNT
TGCTCTTGTCCTTCGGCAGCGTGGCCGCTAGTCATATCGAGGATCAAGCANAACAATTCT
TTATGAAGTGGCCNATCAAACAANCTGGGCCTGTTCTTGGTGTACATCCCCGATTCTG
GTATTAATTATCGACATGTTGCAAATACCCTTTCTGTTTATAGAAGTGTCAAGAGGCTAG
GTATTCCTGACAGTCACATNTGCCCCTAATGCTTGCAGATGATATGGCCTGTAATCCCTA
GAAATCCCAAACCAGCTACAGTGTTTTAGTTCACAANCAATNTGGAACTAAATGGTGTAT
GGGAGAATGATGTGGGGAAGGTGNNATTATAGAAGTTTNTTTGAGGTAAACNGGTGGGAGAA
NNNTTTTTTTTACCNGGGTAATTTAANCTGNGGGAGGGANTCCCCACCCTAAGTANCTTCC
TTCGGG

Sequence 1694

GTCCGCAAGATGACCCAGCTCTCTGACCTACGACACTCTCCGGTTTGCTGAGTTTGAAG
ATTTTCCTGAGACCTCAGAGCCCGTTTGGATACTGGGTAGAAAATACAGCATTTTCACAG
AAAAGGACGAGATCTTGTCTGATGTGGCATCTANACTTTTGNTTTACATACAGGAAAAAC
TTTCCAGCCATTGGGGGGACAGGCCCCACCTCGGACACAGGCTGGGGCTGCATGCTGCGG
TGTGGACAGATGATCTTTGCCCAAGCCCTGGTGTGCCGGCACCTAGGCCGAGATTGGAGG
TGGACACAAAGGAAGGCAGCCAGACAGCTACTTCAGCGTCCTCAACGCATTCATCGAC
AGGAAGGACAGTTACTACTCCATTCACCAGATAGCGCAAATGGGAGTTGGCGAAGGCAAG
TCCATAGGGCCAGGTGGTACGG

Sequence 1695

Sequence 1696

Sequence 1697

CGTCCGAAGGAAGGAAGGACGGCTGAGTTCCCCGACGAGAGACACACCCAGATTTTCC
TGCAGCTTGGGGAGAGGTCCTCCCAGGAGCCTTGGTCCCTCGCCTGCCGGAGTCCTT
AGCCAGGATGGAGGCTGTTGTGAACTTGTACCAAGAGGTGATGAAGCACGCAGATCCCCG
GATCCAGGGCTACCCTCTGATGGGGTCCCCCTTGCTAATGACCTCCATTCTCCTGACCTA
CGTGTACTTCGTTCTCCACTTGGGCCTCGCATCATGGCTAATCGGAAGCCCTTCCAGCT

TABLE 1 280/467

CCGTGGCTTCATGATTGTCTACAACTTCTCACTGGTGGCACTCTCCCTCTACATTGTCTA
TGAGTTCCTGATGTCGGGCTGGCTGAGCACCTATACCTGGCGCTGTGACCCTGTGGACTA
TTCCAACAGCCCTGAGGCACTTAGGATGGTTCGGGTGGCCTGGCTCTTCCTCTCCAA
GTTC

Sequence 1698

Sequence 1699

ACGCGTCCGGAAGAATCTACACTTCTTTGCACCAGAGTATGGAGAAGTCACTAATGTGAC
AACAGCAGTGGACATCTACTCCTTTGGCATGTGTGCACTGGAGATGCCAGTGCTGGAGAT
TCAGGGCAATGGAGAGTCCTCATATGTGCCACAGGAAGCCATCAGCAGTGCCATCCAGCT
TCTAGAAGACCCATTACAGAGGGAGTTCATTCAAAAGTGCCTGCAGTCTGAGCCTGCTCG
CAGACCAACAGCCAGAGAACTTCTGTTCCACCCAGCATTGTTTGAAGTGCCCTCGCTCAA
ACTCCTTGCGGCCCACTGCATTGTGGGACACCAACACATGATCCCAGAGAACGCTCTAGA
GGAGATCACCAAAAACATGGATACTAGTGCCGTACTGGCTGAAATCCCCCAGGCCCTGAT
CTGCGCTGTGGCTGTCCCTGGGACGTGCTGCAGCCCTCCTGTCCCCCCAGTC
Sequence 1700

Sequence 1701

CCCACCGTCCGCGCGCGCGCCCTCGCCTCGGCCGCGCCCTAGCAGCCGACTTAGAACTGG TGCGGACCAGGGGAATCCGACTGATAAATTAAAACAAAGCATCGCGAAGGCCCGCGGCGG GTGNTGACGCGANTGCGATNTNCTGCCCANNGCNTCTTGAATGTCAAAGTTGAANAAANC CAATGAAGCGCGGGTAAACGGCGGGAAGTAACTAATGACTTCTCATTAAGGGTAGCCAAA NGCCCTTCGTCATCTNAATTAAGTTGGACCGCGCANTGAAATNGGATGAAACCNAGANTT CCCACNTGTCCCTACCTACNTAATCCAAGGCGGAAAACCACAAGCCAAAGGG Sequence 1702

Sequence 1703

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Sequence 1704

Sequence 1705

Sequence 1706

TCGCCNCGCGTCCGCTGAAGCAAGAGAATCACTTGAACCCAGGAGGTGGAGGTTGCGTGA.
GCTAAGATCGCGCCACTGCACTCCAGCCTGGGCGACAAGAGTGAAACTCCGTCTTAAAAA
AGCCCATGGCAGGCTGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCA
AGGTGGGCGGATCACAAGGTCAGGAGATCGAGACCATCCTGGCGAACACGGTGAAACCCC
GTCTCTACTAAAAAAAATACAAAAAAATTAGCCAGGCGTGGTCGTGGGCACCTGTAGTCC
CAGCTACTCAGGGGGCTGAGGCAGGAGAATGGCGTGAATCCGGGAGGCGGAGCTTGCAGG
GAGCCGAGATAGTGTCACTCCAGCCTGGGTGACAGAGCGAGACTCCGTCTCAAAA
AACAAAAAGCCCGTGGCAATTAATGGTAAAGGAAACCCGGCTTTTAGTGTAAAGAGGTAA
CATAA

Sequence 1707

Sequence 1708

CACGCGTCCGGGAAGCGGTGCGCTCCGTCACCACGGGAGTGCGGGAATCCGCCGTTTGCG

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Sequence 1710

Sequence 1712

CCACCGTCCGGGCGGCCAGAGGTGCGAGAAGGCCGAGGAGAAGGCCAAGGAGATTGCGAA
GATGGCAGAGATGCTGGTGGAGCTGGTCCGGCGGATAGAGAAGAGCGAGTCGTCGTGAGC
GCGGTCGGCGGTTTCCAGCCAATGGATTCTGGTCAACTGGTGGAGATTGGCTGACACCCT
GGAGAAGCCGAAACCAGAGAGCCTTTTGTTTTCCTTTTTTCCTGTCTATGCTCTGTCTC
ACTTAACACTACGTTTTCTGCTATGGTCTGTGTTGATGACCTCAATATGAGTTTCGATT
GTTAACCGTGTTTTTGTTTGGGAAGTAATTTTGTTTGAAAATGCTCTCACATACAGGAAT
TAGGGCCTAGATTGTAAGCTCTTGCAGCAGTCACATTTGTTCCCGGGCTTTGGTGGTTAT
TTTCTAAATTTTTGAGGTGCCTTTGCTATTTCTTGTGTGACCTGATAGCTTCCCCTG
Sequence 1713

GCGTCCGAGCCTCTGGGGGTGGATCCTGAAAGGTGGTCCAGCCGCCTGGCCCTGCGTGGGACCCTCCACCTGGCAGCAGGGTCTCGCTCTGTCACACAGGCTGGAGTGCAGTGGTGAATCTTGGCTCATCGTAACCTCCACCTCCCGGGTTCAAGTGATTCTCATGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGTGGTGACTTCCAAGAGTGACTCCGTCGGAGGAAAATGACTCCCCAGGTCGCTGCTGCAGACGACACTGTTCCTGCTGAGTCTGCTCTTCCTGGTCCAAGGTGC

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Sequence 1714

GTCGCCACGCGTCCGCAGAAGATTGACAAATCTGAGGGCCGCTTCCATGTCCAGAACCTT
AGCCAGGTGGAGCAGGATGGGCGGACGGGGCATGGACTCCGCAGATCTTCCAAGTTCTGC
TTGAAGGAGCACAAAGCCCTCAAGACGTTAGGCATCATCATGGGCACTTTCACCCTCTGC
TGGCTGCCCTTCTTCATCGTTAACATTGTGCATGTGATCCAGGATAACCTCATCCGTAAG
GAAGTTTACATCCTCCTAAATTGGATAGGCTATGTCAATTCTGGTTTCAATCCCCTTATC
TACTGCCGGAGCCCAGATTTCAGGATTGCCTTCCAGGAGCTTCTGTGCCTGCGCAGGTCT
TCTTTGAAGGCCTATGGCAATGGCTACTCCAGCAACGGCAACACAGGGGAGCAGAGTGGA
TATCACGTGGAACAGGAGAAAAAAAAAC

Sequence 1715

CCCCGTCCGCTTTGTTNATCTAAAGGCTTNAGTCCCATTTTTTATACGTTGTATTTT
AAAAACGTTTGAAAGGAGTCTTACACCTGTATCATGAAAACTGAATCCTTTTGAAATACC
ACTATATGAAGAGAGAGAGATGAAATTTAGTGAACAGAATTTGGAAAAGGTGCTCATAATTTC
ACTATGCAAACTTACCCCAGTCTCTAAAAAAGTAATTTAGATTTAAAGTTCTTTGATGTA
TTTGATTTTCTAAATCTTTATGGTTATGATTTGGAATAAAATGTGCCTAATCCTGTGTTA
CATTCTGTTCTTAAATCTGAATGCCTTCTCATTTAATTCTGAGGAAAATATCACACAAGTG
TCTTCATTGACCTTGAAGAAATGTATATACAGTTGCCTTATAAAACAACATAAATTTAGA
CCATAACTTTTATAGAGAAAAGGGTTTTGTCAAATGTTTTCTGAAAATCTGAGTAATTCAA
AGCATGCCTCTGCCCCCTTTAATA

Sequence 1716

Sequence 1718

CGGACGCGTGGGTGCCGCCGCCGCCGTCGCTGTCGTAGTCGCCGCCGCCGCTGCCGAGA
AAGAGCACGAGCGGGGAAGCCCCAGAGTGAAATCTAGCATCCTGCCGGCTGGTCTGCCG
CCCTCCTTCCTTTTCCCCCCGGCCCCNGTCCCCTCCCNCCGCAGGTGCCATCCGTCGCC
ATNCGCCTCTCTACCCTCNCATCCCCAGGTGAGGGGGGTGAGTTCAGGAAGCGGNNACCC
CNAGGAACCCANCAGGGTCACCATTTGCAGCGCAACATGGCAGGAGCTGAGGAGGGAAT
GATATTCAGTGGCGTTTTTTTCAGGTGAAAGGAGCAGTATGATGATGATGTAGCAGNAAG
CANGATATNATTTCTACAGTANAATTTAATCNTTTCTGGGAGAAATTCTAGCAACANGAA
GATAAAAGGTGGGTAGAGGTTGTCATTCTTTCAACAGGGAGCAGGAGAAC
Sequence 1719

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Sequence 1720

CTGANGCTCGTTTTCGTGAAATTAAGCTTCAGAGGGAAGCCCGNGAAACACAGGAGAGCGAGCGCAAGCCCCCACCATACAAGCACATCAAGGTGAATAAGCCTTACGGGAAAGTCCAGATCTACACAGCGGATATTTCAGAANTCCCTNAGTGCAACTGCAAGCCCACAGATGAGAATCCTTGTGGCTTTGATTCGGAGTGTCTGAACAGGATGCTGATGTTTGAGTGCCACCCGCANGTGTGTCCCGCGGGCGAGTTCTGCCAGAACCAGTGCTTCACCAAGCGCCAGTNCCCAGAGACCAAGATCATCAAGACAGATGGCAAAGGGTGGGGC

Sequence 1721

Sequence 1722

TCGCCACGCGTCCGCTCTTAACACAGAGTCTGCAGCCCCTAACTGACACCCTGTCCTTCC
TCCTAGGAAGTGCTGGACTCCCTGGTCAGCAATGTCAACATTGAGCTGCTCAATGCCCTC
CGCTACCATATGGTGGGCAGGCGAGTCCTGACTGATGAGCTGAAACACGGCATGACCCTC
ACCTCTATGTACCAGAATTCCAACATCCAGATCCACCACTATCCTAATGGGATTGTAACT
GTGAACTGTGCCCGGCTGCTGAAAGCCGACCACCATGCAACCAA

Sequence 1723

Sequence 1724

Sequence 1725

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Sequence 1726

CCNCGCGTCCGGAGCCGAGAGTGTGTGGAGCAGTTACAGCTGGAAGACCGGGTCCTCTGC
CTCCACAGTAGATGGCTGAATCCTCTATGCGGGACTGGCAAATGGCACTGTGGTCACCTT
CAACATAAAGAACAACAACGACTTGAGATCTTTGAATGCCATGGCCCTCGGGCAGTCAG
CTGTCTTGCTACAGCTCAGGAAGGTGCCCGAAAACTGCTGGTCGTGGGGTCTTATGACTG
CACAATTAGTGTACGCGATGCCCGGAATGGACTGCTCCTCAGAACTCTGGAGGGCCATAG
CAAAACCATTCTTTGCATGAAGGTGGTGAATGATCTCGTGTTCAGTGGCTCCAGTGATCA
GTCAGTCCATGCTCACAACATTCACACTGGTGAGCTCGTGCGGATCTATAAAGGTCACAA
TCATGCAGTGACTGGTGAATATCCTAGGAAAAGTGATGGTGACTGCTTGCCTGG
Sequence 1727

CNCGCGTCCGGATNAATATTTTCATCCCTGAGGTTAACAATTACCATCAAAATGTTTTGT
GGAGACTATGTGCAAGGAACCATCTTCCCAGCTCCCAATTTCAATCCCATAATGGATGCC
CAAATGCTAGGAGGAGCACTCCAAGGATTTGACTGTGACAAAGACATGCTGATCAACATT
CTGACTCAGCGCTGCAATGCACAAAGGATGATGCAGAGGCATACCAGAGCATGTAT
GGCCGGGACCTGATTGGGGATATGAGGGAGCAGCTTTCGGATCACTTCAAAGATGTGATG
GCTGGCCTCATGTACCCACCACCACTGTATGATGCTCATGAGCTCTGGCATGCCATGAAG
GGAGTAGGCACTGATGAGAATTGCCTCATTGAAATACTAGCTTCAAGAACAAATGGAGAA
ATTTTCCAG

Sequence 1728

Sequence 1729

TCGACCACGCGTCCGATCCTGGATCTGGAGAGAGAGCTCTCCAAGCAAATCAACGTGTGC
CTCTGAGCCAGATGACGGGGTGGGACCCCGGTTAGTAAGGACCGGGCGCCCAGTGGCTAA
GGCGGTGCCCTGGTGACCAAGGAGAGCCAGACCTGTTGCTCAGGCCGAGCTCCTGGTTGC
CAGCGAGTTACCACGGGACCAGTCGCGTGTATGGCTGAGACTCATTCCCAGTTTCCAGGG
CCCGGTATTTGGACACTAGTTGCCAAGTCTGGGGCCTGGGGATTTTAGGGACCAGCGGTT
GTGACCATCTTTCCTGAGCACCAAGGGCTTCCCCTTTTGTTGCCAAAAAAGGTAGTTCTCG
CGCTTGCTAGGCTGGCCTCTCTTGCCTCCCCTTTGGCCGGGC

Sequence 1730

CTGNGAGTTAAATTGGTCCAGAAACAGTTATGACCCTCTTTATACTGCCAAGAAATACGC AGTCCCAGCCTTGGAAGCACACTGTGTAGAATTTCTCACCAAACATCTTAGGGCAGATAA TGCCTTTATGTTACTTACTCAGGCTCGATTATTTGATGAACCTCAGCTTGCTAGTCTTTG TCTAGATACAATAGACAAAAGCACAATGGATGCAATAAGTGCAGAAGGGTTTACTGATAT TGATATAGATACACTCTGTGCAGTTTTAGAGAGAGACACACTCAGTATTCGAGAAAGTCG ACTTTTTGGAGCTGTTGTACGCTGGGCAGAAGCAGAATGTCAGAGACAACAATTACCTGT

TABLE 1 286/467

GACTTTTGGGAATAAACAAAAGTTCTAGGAAAAGCACTTTCCTTAATCCCGGTTCCCAC TGATGACAATTGAGG

Sequence 1731

Sequence 1733

Sequence 1735

GCGTCCGAAAATACACTGCGACTCTTTCGAGGCCCTGTAATTGGAATGAGTCCACTT
TAAATCCTTTAACGAGGATCCATTGGAGGGCACTTCCAGAATACCTCCCCCAGCGCC
CGCTGCCAGCCCCACACCAGGTGTGAGAACCAAGGTCTGGTGGAGGCAGCTCCAGGCACT
GCCCAGTCCGACACACCTGCAAAAATCCATTAGAGCCACTGCCCCCAGAGATG
Sequence 1736

TABLE 1 287/467

GCCCCCGGC

Sequence 1737

ATCCTTTTGCCTAAAGATGTAAACAAAACTCAAGACAGAAGGAATCAGGGAATATGTGCT
NTTGTGNGCATCTTGTTTACATTTNGGGATCAANTGATGGCAAAAGAAGTAATGAGACCA
CTNNAAATTGTTTTNCANTTGNNTTTAAAANACCAGGGTTCCTCATTTTCTTTGATTTTG
NAAGTTTTAACAATTGACCTTCTTAAGNGACATTCTCTTTCAAAAAAGANANGTAAANCA
GGNGAAATGAAGGGTGGNTGGGGAAA

Sequence 1738

CCGGCTCATTCCCTGAGGCCGGCCCGCGTCCCGTCAGGGCGCCGCGGGGGTTAGCGCGG GGTCAGCGGAGGTCAGCAGCAGCAGCGGCTCCGAGGGCGCGGGGCGCAGGA TGTACACGCTGCTGTCGGGCTTGTACAAGTACATGTTTCAGAAGGACGAGTACTGCATCC TGATCCTGGGCCTGGACAATGCTGGGAAGACGACCTTCCTGGAGCAGTCGAAAACCCGAT TT

Sequence 1739

Sequence 1740

Sequence 1741

Sequence 1742

Sequence 1743

GTGATTAGAAGTAAGCGNTGATGAGGCTGAAGAAAAGGAAGACAAAACTGAGTACTTGGA GGAACGAAGAGTAATGGGATATCCAATAAACTGAGAATGTTTCTTCACAATCTCCTTTAT TCTTCGTTCCTCCAAGTACTCAGTTTGGTCTTCTTTCAGGTAGGAACGTGATAAAGAA

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Sequence 1744

CGATTTCTTTGTTGGACAACCCAGCTGGGGCTAGGAATGGTTCAGAAGGTTTAAGGCCGG
AANGGNAATGAAGGGCCCGGCGCTAACCCTCTAGGGACCTGTTTTGCTTCTGTTTAAA
CCAAATGGGCAGTCTGTCATTACACACACCCTGNGTCTTCATATGTGGCTCGCCAGTATA
ATGGAATGTGCTTACAAGGGCCAGCAGGAGTGCCTGGTCGAGACGGGAGCCCTGGGGCCA
ATGGCATTCCGGGTACACCTGGGATCCCAGGTCGGATTCAAAGGAGAAAAGGGGG
AATGTCTGAGGGAAAGCTTTNAGGAGTCCTGGACACCCAACTACAAGCAGTGTTCATGGA
GTTCATTGAATTATGGCATANATCTTGGGAAAANTGCGGAGTGTACATTTACAAANATGC
TTTTCAAATAGTTGCTNTAANANTTTTGTTCAG

Sequence 1745

GGACGCGTGGGTGGAAATGTAAACAAGAATAGACTGTTCATTCCTGATGGCTTTTAGTCT
ATACTAACATATTGTTTGTCATGCATCCGAGACTGAAAAGACCCATGCTTTACTGCAGA
CTTGTAGCACTGAATCTCTTATTTCCAGCCTTGGGTCTGGGGGCATTTTGCCTCGTAGCT
GACAGACTTCTTCAGTTTTCCACAATTCAGCAAAATGACTGGCTTCGTGCTCTCTCAGAT
AATGCAGTACATTGTGTAATTGGCATGTGGTCATGGGCGGTAGTCACTGGAATCAAGAAG
AAGACTGACTTTGGAGAAATCATTTTAGCTGGATTTTTAGCCTCTGTTATTGATGTAGAC
CACTTTTTTCTAGCTGGATCCATGTCTTTAAAGGCTGCTTTGACTCTCCCGCGAAGACCT
TTCCTTCACTGTTCTACTGTGATTCCCGTTGTGGTTCTGACCCTGAAATTTACTATGCAC
CTTTTCAAGCTCAAAGACTCATGGTGCTTTCTTCTGGGATGGTATTTATATCC
Sequence 1746

Sequence 1749

TABLE 1 289/467

GCCCNTCCCGACCTCCAGCTCATGGTGTCTGGGGCCTGCGGCTAGACTCTTGGAACATT
CTGGAACTCTCCTTTCCTGGCTGGGGCTCTGACCACAAACTCCCCTCCAGGCTGCCCC
TGGGACATGGTGGTGATGTGGGTGCAGGAGCCAGTGTCTGTTGTCGGGACTCGCAAGTGC
CCTCATCACAGCCACCCCCACCACGAGTGTCTCCCCAGTGCAGACTCAAGTTATGCTTGA
AATGAAAAAGTCTATCTGGTAGTGGGTAAACGTAGACCTGGCACTGTTCCACGCGGGCGC
CCCAAGCCTGCCACTCCTTGTCCCTGCCTCCCTGGGCTCCCGAGGATAGGCACCACTGTA
TCCTCCAGCTCCTTCCTTCCTCCCCCAGGAACACGGAGGCCACCGAGGGGGCTGGGCCT
ATCAGGAGGACACAGGCTGCAGCCTGGCACCCACCCCTCCATCTTCACCCCACATGGAAG
ACTTGTCTTCAAC

Sequence 1750

Sequence 1751

GGGCATGCTCATAGGCACAGCTGTTGGTCAGTATGCCAATAACATCACACTTTGGATCTT
TGCAGTCACTGCAGGCATGTTCCTCTATGTAGCCTTGGTGGATATGCTTCCAGAAATGTT
GCATGGTGATGGTGACAATGAAGAACATGGCTTTTGTCCTGTGGGGCAATTCATCCTTCA
GAATTTAGGATTGCTCTTTGGATTTGCCATTATGCTGGTGATTGCCCTCTATGAAGATAA
AATTGTGTTTGACATCCAGTTTTGACCTTTCCCAGTAATCACTGTTGATTACGAGAATGT
TACCATGCAGCTTTGCATCTGTTCCTTGTACTGTATGCACATTGCTCAAAGGAAAGTCAG
TGGCTTGCACTACTACAAGTTTCATAGATTTGAGCCTAACCACAAGAGGCTGGTGCTTA
GTACTGTTTTCCCTGCACGTAGGGGTCTTTTAAAAAATATAAAAGCTTGTGATAAAAGAGAGG

Sequence 1752

CTGGTTCAGCAGCCGCCCACCCACCTCTGAGTCTGACCTGGAACCTGCCACAGATGGGCC
AGCCTCCGAGACCACCTACCCTCAGCCCAGAGGCCACCACCTTTAATGACACCAGAATCCC
TGATGCAGCTGGTGGCACGGCCGGCGTGGGTACCATGCTTCTGTCCTTTGGGATCATCAC
GGTGATAGGCCTGGCTGTGGCCTTGGTTTTGTACATCAGGAAGAAGAAGAGGCTGGAGAA
GCTACGCCACCAGCTCATGCCCATGTACAACTTCGACCCCACGGAGGAACAAGATGAGTT
GGAGCAGGAGCTGCTGGAGCATGGGCGGGACGCCGCCTCTGTACAGGCTGCTACTTCTGT
GCAGGCCATGCAGGGCAAGACTACTCTGCCCTCCCAGGGCCCACTCCAGAGACCCAGCCG
GCTTGGTGTTTACCCGATGTGGCCAATGCCATCCATGTGTGAGTGGCCTGGGACAAGC
Sequence 1753

GTCGCCCGCGTCCGGTGCTCTCATGTCATCTCAGAGTTCCAGCTTATCAGAGGCATGTA
GCAGGAGGCTTATTCCAGCCATAACTGGGCTCTACCTCCAGCCTCCAGAAGTAATCCCC
AACCTGCATATCCTTGGGCAACCCGAAGAATGAAAGAAGCTATAAAACCCCCTTTGA
AAGCTTTCATGAAGCAGAGGAGGATGGGTCTGAACGACTTTATTCAGAAGATTGCCAATA
ACTCCTATGCATGCAAACACCCTGAAGTTCAGTCCATCTTGAAGATCTCCCAACCTCAGG
AGCCTGAGCTTATGAATGCCAACCCTTCTCCTCCACCAAGTCCTTCTCAGCAAATCAACC
TTGGCCCGTCGTCCAATCCTCATGCTAAACCATCTGACTTTCACTTCTTGAAAGTGATCG
GAAAGGGCAGTTTTGGAAAGGTTCTTCTAGCAAGACCA

Sequence 1754

TCGCCCGCGTCCGGACTGATCATAAACCATGCTGGTATTGCACCTTCTGGAACTATGGG CTTGAGAAAACCCCCAGGATCACTTCTCCTTGGCTTCCTTATTTTCTTGAGGCAGGTCGC ACGTTCTACCTGCCCAAGACGTGTGATATCAGCTTCTCAGATCCAGACGACCTCCTCAAC TTCAAGCTGGTCATCTTGTCCTGATGAGGGCTTCTACAAGAGTGGGAAGTTTGTGTTCAG